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Haematological and Biochemical Changes in Response to Stress Induced by the Administration of Amikacin Injection by Autoinjector in Animals

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ABSTRACT

The drugs administered by autoinjectors, may act fast reducing the morbidity and mortality in critical and emergency situations. Amikacin drug cartridge was developed for the autoinjector as an antibacterial drug for critical situations and its tolerability was studied. Rats were given either 3 doses or 7 doses on consecutive days by the autoinjector (intraperitoneal, 63 mg/mL). Blood was withdrawn on the 4th day (3 doses) or the 8th day (7 doses), and haematological and biochemical parameters were studied. All the parameters studied were within the limits and did not show any significant difference when compared with the control. Rabbits were given 3 doses of two concentrations (intramuscular, 63 or 250 mg/mL) and on the 4th day blood was withdrawn for the haematological and biochemical estimations. 63 mg/mL cartridge did not show any significant change while 250 mg/mL cartridge showed significant change in the haematological and biochemical parameters. This study showed that intraperitoneal injection of amikacin by the autoinjector designed for intramuscular injection was well tolerated by the rats. In the rabbits, low dose (63 mg/mL) was tolerated while the higher dose, which is an adult human dose (250 mg/mL) showed significant changes.

Keywords: Autoinjector, antibacterial, amikacin, emergency, critical situation

1. INTRODUCTION

A number of critical and emergency situations occur in which the individual requires first aid measures. When a qualified medical person is not available, the recommended drug has to be administered by self or by a trained individual to reduce the morbidity and mortality. Nerve agent exposure in a war scenario and other organophosphorus pesticide poisoning require immediate administration of atropine sulphate and pralidoxime chloride to reduce the mortality[1]. These drugs can be administered by a self administrable device, the autoinjectors[2,3]. In comparison to manual intramuscular injection the autoinjector can deliver the drugs by deep intramuscular injection with a spray effect, increasing the area, thereby faster drug absorption. The needle is not visible in these autoinjectors and the injection will be painless, convenient and well suited for mass casualty situations. Healthy volunteers were administered atropine and pralidoxime chloride through the autoinjectors and it was observed that the absorption of the drug was faster by the autoinjector[4].

Only for a few emergency situations the recommended drugs are available as autoinjectors. In seizures, anticonvulsants are required to reduce the severity and prevent brain damage. Midazolam, a water-soluble benzodiazepine agonist has been developed as an autoinjector for intramuscular injection[5]. In emergency situation like status epilepticus, diazepam has to be administered immediately. The absorption of diazepam given by the autoinjector was found to be faster and can be administered safely and reliably[6]. Severe allergy leading to anaphylaxis is common due to food, exercise, hymophtera venom and latex. Epinephrine is the drug of choice for anaphylaxis and it has to be administered promptly using an autoinjector[7,8]. Migraine is characterised by throbbing headache. Sumatriptan is one of the preferred drugs for migraine and an autoinjector has been developed as an alternative to sumatriptan injection[9].

In military service life during training and operation, low intensity conflicts, road accidents and also natural disasters situations may occur in which the individual may be seriously injured requiring an analgesic and an antibacterial drug for field administration by self or by an authorised person[10]. The purpose of this study is to develop amikacin drug cartridge for the reusable autoinjector and to study the effect on haematological and biochemical changes in response to stress induced by its administration through the autoinjector in rat and rabbit (rodent and non rodent).

2. MATERIALS AND METHODS

2.1 Animals

Randomly bred Wistar male rats (120 - 200 g) and New Zealand White Rabbits of both sexes (1750 - 2250 g), bred and maintained at Biomedical Research Unit and Laboratory Animal Centre (BRULAC) of Saveetha University were used for the study. The rats were kept in polypropylene cages (3 per cage) with sterilised and dry paddy husk as a bedding material. The rabbits were housed in stainless steel cages (1 per cage). The animals were fed with commercial laboratory animal feed (Tanuvas, Chennai) and purified water *ad libitum*. The

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care and maintenance of the animals were as per the approved guidelines of the 'Committee for the Purpose of Control and Supervision of Experiments on Animals' (CPCSEA, India). This study has the approval of Institutional Animal Ethical Committee of Saveetha University (SU/SMC/RD/010/2012; Dt. 21 February 2012).

2.2 Chemicals and Drugs

The amikacin drug cartridge was developed with the collaboration of M/s Neon Laboratories (Mumbai), who are the technology holders for the development of nerve agent antidote cartridges for the autoinjector (Fig. 1). The amikacin cartridge was made similar to the atropine sulphate drug cartridge. The cartridge contained 250 mg/mL of amikacin as amikacin sulphate with stabilisers. The drug volume was 2.3 mL to 2.4 mL and upon ejection by the autoinjector, 2.1 mL to 2.2 mL would be delivered. The other QAQC parameters were as per the nerve gas antidote drug cartridge[3]. The other chemicals were either Indian Pharmacopoeia grade or analytical grade, purchased from standard companies. Autoinjectors produced by M/s Sigma Engineering (Hyderabad), a technology by Defence Research and Development Organisation (DRDO) and has an option to select full dose delivery or partial dose delivery (dual dose autoinjector) was used.

2.3 Experiments in Rats

2.3.1 Autoinjector Usage

The tolerance of the amikacin autoinjector was studied by injecting the drug intraperitoneally in rats. For this the drug cartridge was diluted 1:4. From the cartridge 1.75 mL of the drug solution was withdrawn under a laminar flow and 1.75 mL sterile saline was injected back to make the concentration to 63 mg/mL. The drug cartridge was loaded in the autoinjector with the plastic clip restrictor (Fig. 1). This would allow only partial volume of the drug (about half) to be injected and restricting the ejected needle length to half. The rats were held firmly on the surgical table with its back on the table. The autoinjector was unlocked and positioned gently on the lower abdomen vertically. The trigger button was pressed and held on to the abdomen for 10 s. The autoinjector was then removed gently and the needle length that was protruding from the cartridge was measured. The drug cartridge was weighed before and after injection to estimate the quantity of the drug injected. For the manual injection the drug solution removed from the cartridge was diluted 1:4 with sterile normal saline (63 mg/mL) and 1 mL was injected intraperitoneally for each rat.

(a) (b)

Figure 1. Autoinjectors with drug cartridges (a) Autoinjector with the restrictor for the partial delivery of the drug with partially ejected needle. (b) Autoinjector with fully ejected needle.

2.3.2 Experimental Groups

The first experiment was carried out by delivering the drug through the autoinjector for 3 consecutive days. The second experiment was carried out by delivering the drug through autoinjector for 7 consecutive days. The following were the groups of this study. For each group 6 rats were used.

Group A : Control,

Group B : Amikacin injection, 63 mg/mL cartridge for 3 days by autoinjector,

Group C : Amikacin injection, 63 mg/mL for 3 days by manual injection,

Group D : Amikacin injection, 63 mg/mL cartridge for 7 days by autoinjector,

Group E : Amikacin injection, 63 mg/mL for 7 days by manual injection.

Group F : Amikacin injection, 63 mg/mL cartridge for 7 days by autoinjector, followed by 7 days recovery

Group G : Amikacin injection, 63 mg/mL for 7 days by manual injection, followed by 7 days recovery.

2.3.3 Sample Collection

The animals were weighed daily, and general behaviour, food intake and water intake were recorded. Twenty four hours after the last injection (4^{th} or the 8^{th} day) blood was withdrawn from the orbital sinus of the rats after anaesthetising the animals with anaesthetic ether. Blood was collected in two tubes with anticoagulant (Na_2 EDTA) and without anticoagulant. After the collection of the blood the animals were sacrificed with over dose of anaesthesia. Vital organs viz., heart, spleen, kidney, testis, liver and lung were excised, blotted free of blood, weighed and preserved in formalin solution.

2.4 Experiments in Rabbits

2.4.1 Autoinjector Usage

The tolerance of the amikacin autoinjector was studied by injecting the drug intramuscularly in rabbits. Two doses were given to the rabbits (63 mg/mL and 250 mg/mL cartridge). For the 63 mg/mL, the drug cartridge was diluted 1:4 as mentioned above. The drug cartridge was loaded in the autoinjector with the plastic clip restrictor. This would allow only partial volume of the drug (about half) to be injected and restricting the ejected needle length to half. The rabbits were held firmly on the

surgical table with their side on the table. The autoinjector was unlocked and positioned gently on the thigh muscle vertically. The trigger button was pressed and held in position for 10 sec. The autoinjector was then removed gently and the needle length that was protruding from the cartridge was measured. The drug cartridge was weighed before and after injection to estimate the quantity of the drug injected. For the 250 mg/mL, the cartridge was used as such.

2.4.2 Experimental Groups and Sample Collection

Twenty four hours prior to amikacin administration, the rabbits were anaesthetised with ketamin (30 mg/kg, i.m.) and blood was withdrawn from orbital sinus. Thereafter, the injections were given by autoinjector (63 mg/mL or 250 mg/mL cartridge). The animals were weighed daily, and general behaviour, food intake and water intake were recorded. Twenty four hours after the last injection (4^{th} day) blood was withdrawn from the orbital sinus of the rabbit after anaesthetising the animals with ketamin. Blood was collected in two tubes with anticoagulant (Na_2 EDTA) and without anticoagulant. The rabbits were rehabilitated after that. For each dose four rabbits were used.

2.5 Haematological Parameters

The whole blood was used for the estimation of haemoglobin (Hb), packed cell volume (PCV), red blood cell count (RBC) and white blood cell count (WBC). Beckman Coulter Cell Counter (UK) was used for the analysis. The analyses were done at Regenix Super Specialty Laboratory (Chennai) as per the equipment manufacturer's instruction.

2.6 Biochemical Parameters

Serum was separated from the blood, and glucose, urea, creatinine, aspartate aminotransferase (AST), alanine amonitransferase (ALT), gama glutamyl transferase (GGT) and lactic dehydrogenase (LDH) were estimated. For the analyses Roche Modular EVO 9000 autoanalyser (USA) was used. The analyses were done at Regenix Super Specialty Laboratory (Chennai) as per the equipment manufacturer's instruction.

2.7 Organ to Body Weight Ratio

The organ to body weight index (OBWI) in rats was calculated as a ratio of organ weight divided by body weight and multiplied by 100. The tissues were fixed in formalin solution and preserved for histological studies.

2.8 Statistical Analysis

All the parameters were analysed using one way analysis of variance and compared with control using Dunnett's test in the rat experiment. Paired 't' test was used in the rabbit experiment. A probability of 0.05 and less was taken as statistically significant. The analysis and plotting of graphs were carried out using SigmaPlot 12 (Systat Software Inc., USA).

3. RESULTS AND DISCUSSION

3.1 Experiments in Rats

In one rat full dose of 500 mg of amikacin was injected intraperitoneally through the autoinjector (full needle length). The animal died within 1 hour. In two rats partial dose of 250 mg was injected intraperitoneally (partial needle). The delivery of the drug was perfect and the animals did not react. The rats survived after the first dose and a second dose of 250 mg was administered intraperitoneally through the autoinjector the next day. Both the rats died within 4 hours. Hence, the cartridge was diluted 1:4 (63 mg/mL) and 3 injections were given on consecutive days. As the animals responded very well a second experiment was carried out by administering the drug for 7 days consecutively. Based on the amount of solution injected and the weight of the animal the injected dose was calculated. Four autoinjectors were used in this study and the dose injected per day for the rats was 546.0 ± 15.5, 515.3 ± 23.6, 496.6 ± 39.7 and 494.2 ± 26.1 (mean ± SE) mg/kg respectively for the four autoinjectors. The dose administered was not significant from each other. The average dose injected in the rats was 511.5 ± 16.2 (mean ± SE) mg/kg. Using the restrictor the effective needle length was 15.54 ± 0.09 mm (partial needle). Without the restrictor the effective needle length was 26.42 ± 0.09 mm (full needle).

The food consumption, water intake, general behaviour and body weight of the rats did not show any significant difference among the groups. Upon opening the abdomen no sign of bleeding or injury was observed, due to the autoinjector or the manual injection. Figure 2 shows the OBWI of 3 day and 7 day treatment. There was no significant difference between

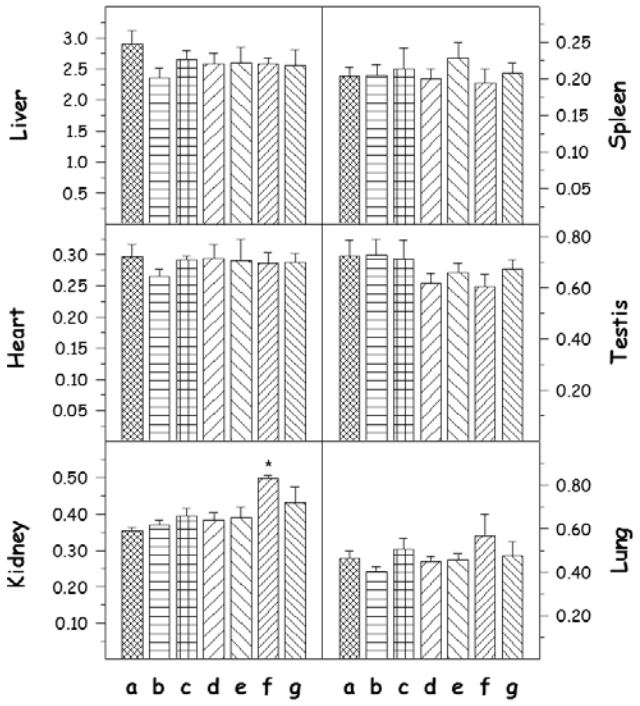

Figure 2. Organ to body weight ratio (g/100 g) of rats after 3 days and 7 days administration of amikacin by Autoinjector and by manual injection.

Note: a = Control, b = 3 days Autoinjector delivery, c = 3 days manual injection, d = 7 days Autoinjector delivery, e = 7 days manual injection. f = 7 days Autoinjector delivery with 7 days recovery, g = 7 days manual injection with 7 days recovery. Mean ± SE, n =6. *Significantly different from control.

the control group, the groups of autoinjector and the groups of manual injection, except the kidney weight was significantly higher in the autoinjector 7 day recovery group. Figure 3 shows the level of Hb, PCV, RBC count and WBC count. No significant difference was observed between all the groups. The serum parameters viz., glucose, urea and creatinine did not show any significant difference compared to control (Fig. 4). Similarly the enzymes AST, ALT, GGT and LDH also did not show any significant difference from the control (Fig. 5).

3.2 Experiments in Rabbits

One autoinjector was used for administering the amikacin to the rabbits. The average dose injected per day for the rabbit was 56.0 ± 4.4 mg/kg (mean ± SE) with 63 mg/mL cartridge and 189.2 ± 8.2 mg/kg (mean ± SE) with 250 mg/mL cartridge. Using the restrictor the effective needle length was 15.79 ± 0.11 mm (partial needle). The food consumption, water intake, general behaviour and body weight of the rabbits did not show any apparent change in the 63 mg/mL cartridge group but the 250 mg/mL cartridge group showed sluggish activity. Figure 6 shows the level of Hb, PCV, RBC count and WBC count. No significant difference was observed in the 63 mg/mL cartridge group between the pre and post administration of amikacin, except an increase in WBC count. The 250 mg/mL cartridge group showed a significant decrease in Hb, PCV and RBC count, and no change in WBC count. The serum parameters viz., glucose, urea and creatinine did not show any significant difference compared to pre administration levels in the 63 mg/mL and 250 mg/mL cartridge groups, but the creatinine level was significantly increased in the 250 mg/mL cartridge group in the post administration (Fig. 7). The serum enzymes AST, ALT, GGT and LDH also did not show any significant difference in post administration compared to the pre administration (Fig. 8).

4. DISCUSSION

Aminoglycosides are potent bactericidal antibiotics that act by binding to 30 s ribosomal subunits. They are particularly active against aerobic, gram-negative bacteria and act synergistically against certain gram-positive organisms. Amikacin is a safer antibiotic and effective against gentamycin resistant organisms[11]. Amikacin sulphate is water soluble and stable, and hence used for preparing the drug cartridge. Since the adult intramuscular dose is 500 mg the cartridges were made with the same dose and diluted for the animal usage. The front septum of the cartridge is made of silicon (~30 shore hardness) and withdrawing the liquid from the cartridge and injecting sterile saline using a 22 gauge needle was effective, as there was no leak while ejecting the

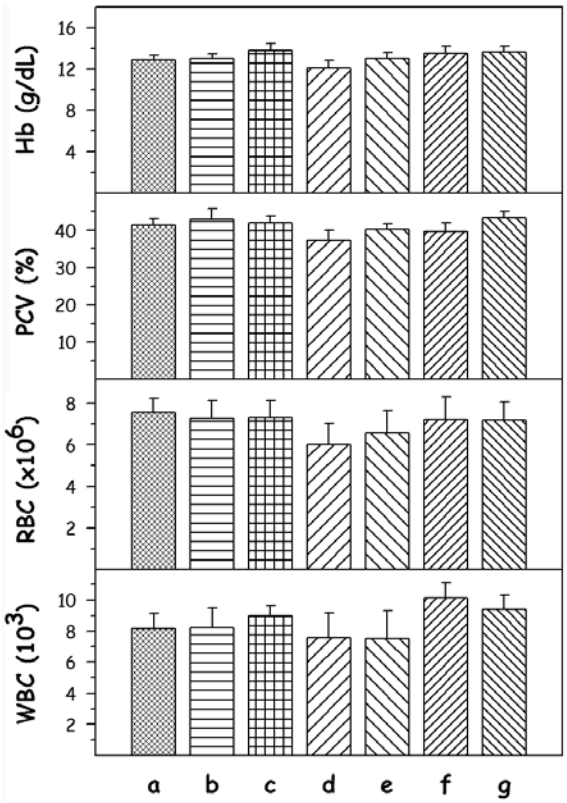

Figure 3. Haematological parameters of rats after 3 days and 7 days administration of amikacin by Autoinjector and by manual injection.

Note: a = Control, b = 3 days Autoinjector delivery, c = 3 days manual injection, d = 7 days Autoinjector delivery, e = 7 days manual injection. . f = 7 days Autoinjector delivery with 7 days recovery, g = 7 days manual injection with 7 days recovery. Mean ± SE, n =6.

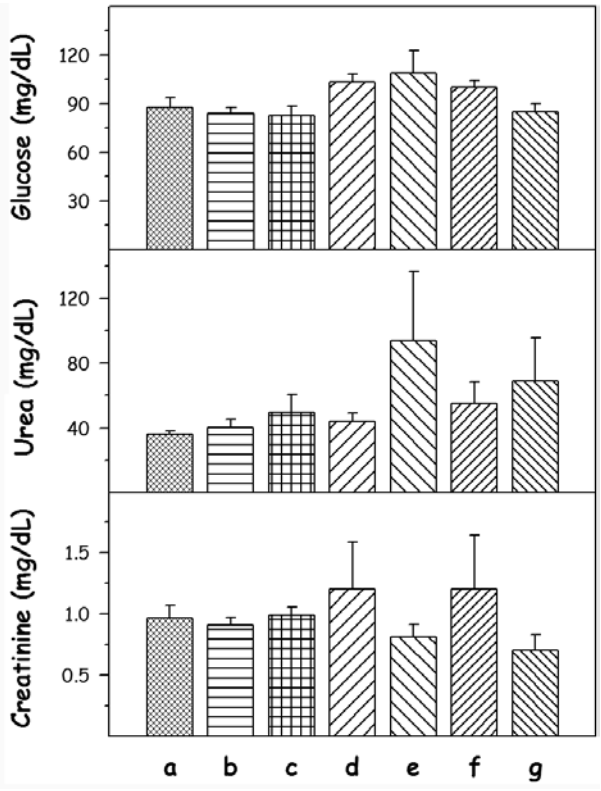

Figure 4. Biochemical parameters of rats after 3 days and 7 days administration of amikacin by Autoinjector and by manual injection.

Note: a = Control, b = 3 days Autoinjector delivery, c = 3 days manual injection, d = 7 days Autoinjector delivery, e = 7 days manual injection.. f = 7 days Autoinjector delivery with 7 days recovery, g = 7 days manual injection with 7 days recovery. Mean ± SE, n =6.

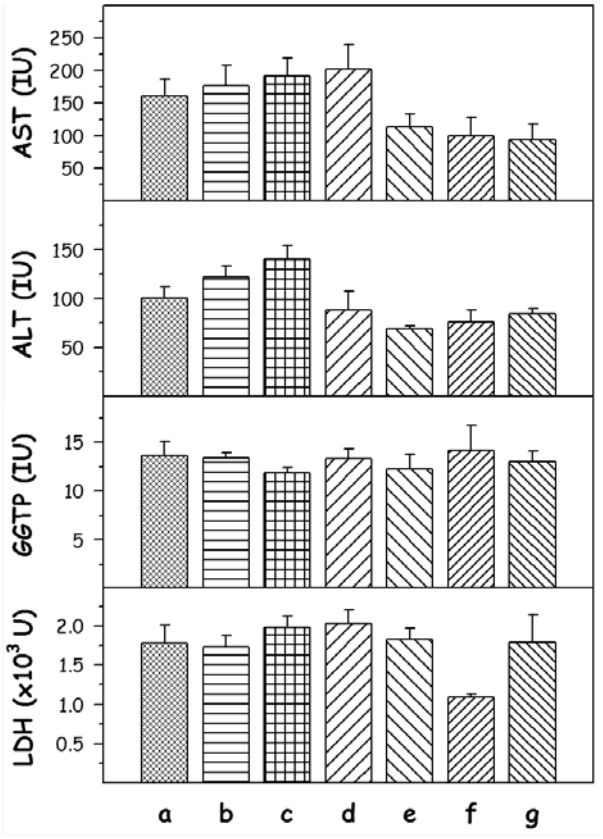

Figure 5. Serum enzyme levels of rats after 3 days and 7 days administration of amikacin by Autoinjector and by manual injection.

Note: a = Control, b = 3 days Autoinjector delivery, c = 3 days manual injection, d = 7 days Autoinjector delivery, e = 7 days manual injection, f = 7 days Autoinjector delivery with 7 days recovery, g = 7 days manual injection with 7 days recovery. Mean ± SE, n =6.

liquid from the cartridge by the autoinjector. The autoinjector with the provision for two doses also functioned satisfactorily. The full dose is expected to deliver a volume of 2.1 to 2.2 mL and the new design of a restrictor in the autoinjector delivered a partial volume of 1.2 to 1.3 mL. The four autoinjectors used in this study also showed same quantity of drug delivery. The injectable needle length was within the range and recommended for the autoinjector devices[12,13]. The autoinjectors meant for intramuscular injection in human being was used in the study with a modification of two volume deliveries - full volume injection and partial volume injection. In the partial volume injection the needle length is in the range of 15 mm – 16 mm. It is not possible to give intramuscular injection in rats as the muscle mass is small. Hence intraperitoneal injection was used to study whether the forceful injection cause any tissue injury in the abdomen. But, in rabbits as the muscle mass is thicker intramuscular injection was given.

The reported LD_{50} of amikacin is 3.5 g/kg by intraperitoneal injection in rat (Material Safety Data Sheet). Since the human dose is close to the LD_{50} of rat the full dose of 500 mg and the partial dose of 300 mg (2 doses) could not be tolerated by the rats. But, a drug like atropine sulphate was

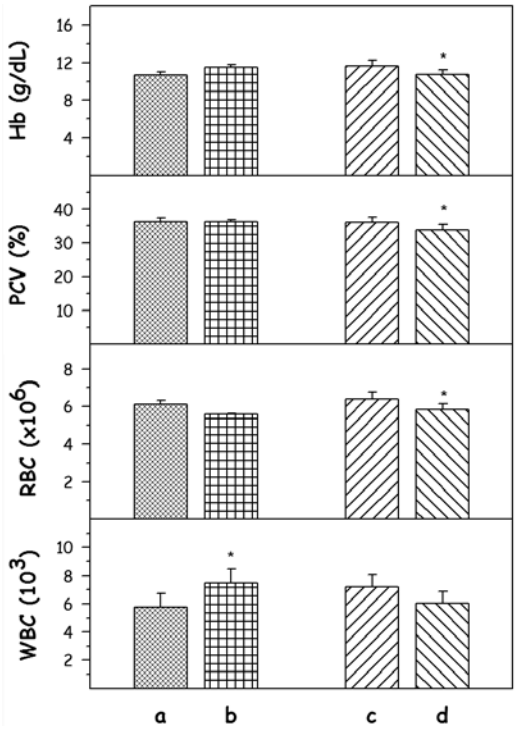

Figure 6. Haematological parameters of rabbits after 3 days administration of amikacin by Autoinjector.

Note: 'a' before (Control) and 'b' after 63 mg/rabbit of amikacin administration by Autoinjector. 'c' before (Control) and 'd' after 250 mg/rabbit of amikacin administration by Autoinjector. Mean ± SE, n =4, *Significantly different from respective control by paired 't' test.

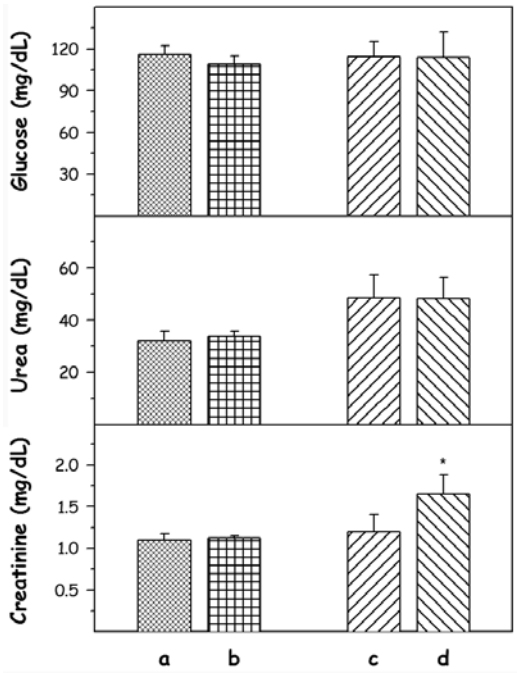

Figure 7. Biochemical parameters of rabbits after 3 days administration of amikacin by Autoinjector.

Note: 'a' before (Control) and 'b' after 63 mg/rabbit of amikacin administration by Autoinjector. 'c' before (Control) and 'd' after 250 mg/rabbit of amikacin administration by Autoinjector. Mean ± SE, n =4, *Significantly different from respective control y paired 't' test.

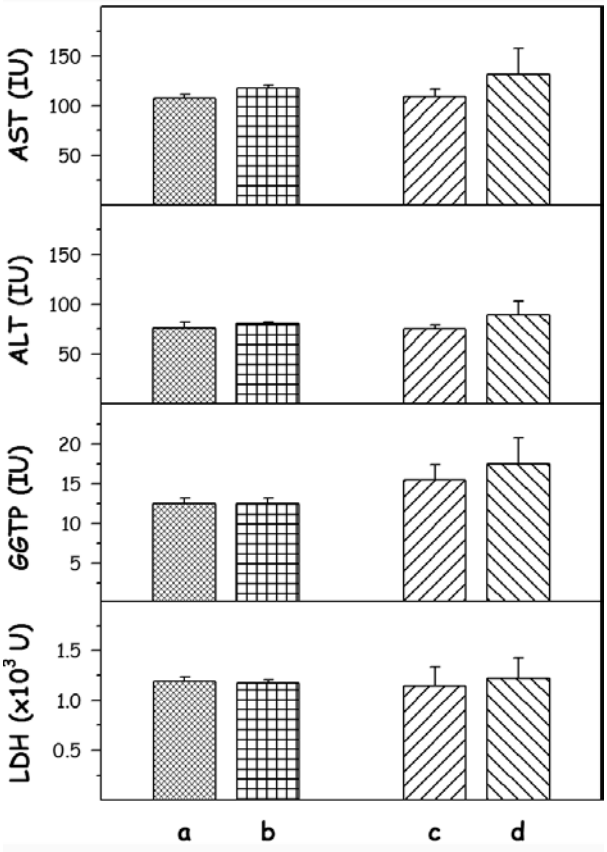

Figure 8. Serum enzyme levels of rabbits after 3 days administration of amikacin by Autoinjector.

Note: 'a' before (Control) and 'b' after 63 mg/rabbit of amikacin administration by Autoinjector. 'c' before (Control) and 'd' after 250 mg/rabbit of amikacin administration by Autoinjector. Mean ± SE, n =4.

tolerated by pigs when the human dose was administered by autoinjectors[14]. In the experimental dose (63 mg/mL cartridge) none of the haematological and biochemical parameters showed any significant difference compared with the control, manual injection and through autoinjector when administered to rat intraperitoneally, showing that the delivery of amikacin through the autoinjector was well tolerated by the rats. Amikacin is known to cause ototoxicity and nephrotoxicity upon long term usage[15]. The serum urea and creatinine levels showed no significant difference, demonstrating that the dose and duration used in this study did not cause nephrotoxicity in rats.

However, in the rabbit intramuscular model the low dose (63 mg/mL cartridge) did not show any effect, but the higher dose (250 mg/mL cartridge) increased the levels of creatinine demonstrating that this dose may cause nephrotoxicity. The haematological parameters did not show any significant change in the rat intraperitoneal injection or the rabbit (63 mg/mL cartridge) intramuscular injection. But the higher dose (250 mg/mL cartridge) showed toxicity. Unlike the rat study, in the rabbit manual injection was not carried out. Never the less, the toxicity may be due to amikacin and not due to the autoinjector force. Since, the delivery of the drugs intramuscularly by autoinjector is expected to be close to intravenous, the higher dose could have caused nephrotoxicity. The reported LD_{50} of amikacin by intramuscular route is 3000 mg/kg and by intravenous route is 260 mg/kg in rabbits. The liver enzymes did not show any significant difference from the control showing that the injection with the autoinjector which delivers the drug with a force did not cause any tissue damage. All the vital organs studied did not exhibit any gross abnormality as the OBWI did not show any significant difference in rat.

This study shows that intraperitoneal injection of amikacin by the autoinjector designed for intramuscular injection was well tolerated by the rats. In the rabbits, low dose (63 mg/mL) was tolerated while the higher dose, which is an adult human dose (250 mg/mL) showed significant changes. The reusable autoinjector with dual dose provision also functioned very effectively. It is also possible to decrease the drug concentration by dilution with normal saline inside the cartridge aseptically and hence the autoinjector can be used for children.

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