The effects of diminazene aceturate on systemic blood pressure in clinically healthy adult dogs

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ABSTRACT

Diminazene aceturate is a commonly used antibabesial agent. It has been postulated that diminazine may induce a decrease in blood pressure and exacerbate the hypotension presented in dogs with babesiosis. This study was undertaken to assess the effect of diminazine aceturate on the blood pressure of healthy dogs. Six healthy German shepherd dogs between 18 and 24 months of age with a mean weight of 30.4 ± 2.75 kg were used. Blood pressure was directly measured at the following time intervals: –5, 0, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 90 and 120 minutes after treatment with diminazine aceturate (4.2 mg/kg) intramuscularly. No statistical difference ($P > 0.05$) was found in blood pressure between any of the time intervals. An increase in heart rate was seen 5 minutes after the administration of diminazine aceturate but no change in blood pressure was evident. This study concluded that diminazene aceturate in its current formulation with antipyrine does not alter blood pressure in healthy adult dogs.

Key words: antibabesial drug, *Babesia*, blood pressure, canine, diamidines, diminazene aceturate.

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INTRODUCTION

Babesia canis is a common tick-transmitted intracellular protozoan parasite of dogs in South Africa. Approximately 11 % of dogs presented to the Onderstepoort Veterinary Academic Hospital have babesiosis[14]. The drugs most commonly used to treat babesiosis are aromatic diamidines (diminazine aceturate) or imidocarb diproprionate[13,16]. In a South African survey, diminazene was the preferred anti-babesial by 88 % of respondents, with 41 % of respondents reporting side-effects to diminazene[6]. Reported side-effects included nervous signs (71 %), anaphylaxis (22 %) and vomition (17 %).

The choice of which antibabesial agent to use has in the past been determined by the severity of the disease symptoms, with severe cases being treated with trypan blue. Trypan blue was used because it is believed to have fewer side-effects and no effect on blood pressure, whereas diminazene aceturate is believed to cause a decrease in systolic blood pressure[12,16] and may exacerbate hypotension in dogs with babesiosis[10]. A number of articles have reported the possibility of hypotension following the administration of diminazene aceturate[1,2,12]; however, they all reference research reported by Wien[19].

Berenil® is formulated as 44.4:55.5 m/m solution of diminazene aceturate and antipyrine as a stabiliser. When diminazene is dosed at 4.2 mg/kg the antipyrine is dosed at 5.24 mg/kg, which is much lower than the pharmacokinetic study ranges of 10–20 mg/kg given iv[4]. It is thus possible that some of the reported side-effects seen with diminazene aceturate administration are due to the effects of antipyrine; however, there are no published reports of antipyrine causing a change in blood pressure.

Wien studied the effects of diminazene aceturate in anaesthetised cats, decerebrated animals and eviscerated organs[19,20]. The author did not use diminazene aceturate, but a closely related aromatic diamidine at a dose of 30–60 mg/kg given intravenously, which is far higher than the recommended therapeutic dose. At these doses, Wien found a minimal effect on cardiac function but that peripheral vasodilatation did occur. Wien also suggested, in an unsubstantiated statement, that diamidines caused hypotension in man[19].

The only other report of hypotension following the administration of diminazene aceturate is by Fussgänger and Bauer[8] of a decrease in blood pressure of 40–80 mm Hg following the intravenous administration of 0.6–2.2 mg/kg diminazene aceturate. Fussgänger and Bauer also cited a personal communication by Evans that 2 mg/kg diminazene aceturate administered intramuscular to humans did not alter blood pressure[8]. Bamgbose indicated that a decrease in blood pressure did occur in dogs following the administration of diminazene aceturate by referring to an 'in press' article by himself[3] that has apparently not appeared in print.

In rats it has been shown that a plasma concentration of 400 μg/mℓ of diminazene aceturate caused a decrease in blood pressure while at 100 μg/mℓ it had no effect on blood pressure[1]. Blaschko *et al.* showed that diamidines had an antihistaminase effect and that an increase in serum histamine occurred following its administration[5]. Steinmann *et al.* showed in rats that a blood concentration of 0.25–25 μg/mℓ diminazene aceturate had weak alpha$_1$ and alpha$_2$ blocking effects, resulted in larger decreases in diastolic blood pressure, and that a reflex tachycardia occurred[15]. It has also been shown that intravenous diminazene aceturate caused a transient decrease in blood pressure in rats[15]. In camels, intramuscular diminazene aceturate had no effect on blood pressure, whereas intravenous administration caused a transient decrease in blood pressure[17].

From the literature it is evident that diminazene aceturate may cause a decrease in blood pressure and that this is probably dependent on the route of administration and dose. This article reports the effect of the intramuscular administration of diminazene aceturate on blood pressure in dogs.

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MATERIALS AND METHODS

This study was approved by the Animal Use and Care Committee of the Faculty of Veterinary Science, University of Pretoria, and the South African Police Services. Six (3 intact males, 2 castrated males, and 1 intact female) German shepherd dogs between 18 and 24 months of age with a mean weight of 30.4 ± 2.75 kg were used in this study. A sample size of 4 was calculated based on a decrease in mean blood pressure of 30 mm Hg (from 110 to 80 mm Hg) with a power of 0.9, a standard deviation of 15 and a $P < 0.05$ (SigmaStat, Jandel Corporation, Chicago). All dogs had not been treated for babesiosis within the last three months prior to commencement of the study.

On the day of the treatment a 20G catheter (Jelco, Johnson & Johnson, Halfway House) was aseptically placed in the dorsal pedal artery and secured into position with tape. Every effort was made to make the dogs comfortable. After placement of the catheter, the dogs were allowed to relax for 5 minutes before calibration samples were taken. This sample was excluded from the analysis of results as it was used to ensure that the system was functional and allowed the dogs more time to become accustomed to the test procedure. Ten minutes was allowed before any readings were recorded. All the dogs assumed sternal recumbency for the duration of the study and the blood pressure transducer was adjusted to the point of the shoulder. If movement artefacts were seen during the recording of blood pressure, recording was stopped until a stable baseline was achieved. Blood pressure was monitored using a tension strain gauge (ProPaq EL80, Propaq Protocol Systems, Beaverton, Oregon). The blood pressure transducer was zeroed and calibrated to a standard mercury column at 0, 50, 100 and 200 mm Hg. The transducer was recalibrate between patients and the drift was no more than 4 %. The blood pressure line was continuously flushed with heparin-saline (5 mℓ/hr, 5 IU/mℓ) (Heparin, Novo-Nordisk). After establishing baseline blood pressures, 4.2 mg/kg diminazene aceturate (Berenil, Intervet South Africa, Isando) was administered intramuscularly into the *biceps femoris* muscle. The blood pressure and heart rate were recorded at the following time intervals: –5, 0, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 90 and 120 minutes after treatment. At each time interval, 5 values for heart rate, systolic, diastolic and mean blood pressure were recorded, and the mean of these values was used in the statistical analysis.

Data was tabulated in a spreadsheet (Excel, Microsoft Corporation, Redmond). Statistical analysis was performed with SigmaStat (Jandel Corporation) and SigmaPlot (SPSS Incorporated, Chicago). The readings recorded for –5 and 0 time intervals were combined for the baseline reading. All data were compared to the baseline reading. Descriptive statistics were used to describe the data. Repeated measures analysis of variance with Tukey's test were used to test for statistical differences. Statistical significance was set at $P < 0.05$.

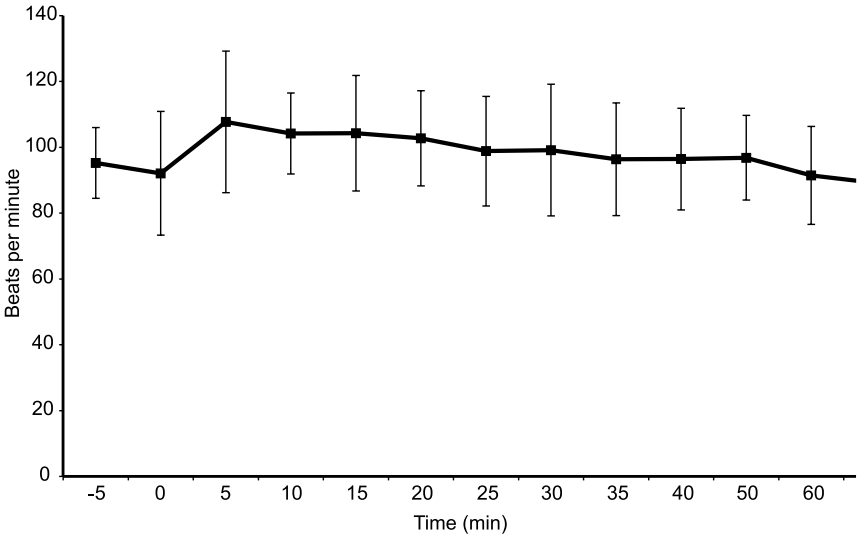

Fig. 1: **Heart rate in 6 dogs after administration of diminazene aceturate. Vertical bars = ±1 standard deviation.**

RESULTS

The mean dose of diminazene aceturate administered was 4.25 ± 0.04 mg/kg. Three readings were lost (two in one animal and one in another) due to catheter occlusion in one instance and two due to disruption of the non-compliant tubing. The heart rate and blood pressure are graphically displayed in Figs 1 and 2. Apart from a tendency for an increase in heart rate 5 minutes after the administration of diminazene aceturate (from 94.8 ± 14.7 to 107.7 ± 21.5), no statistical difference ($P > 0.05$) was observed at any time. Blood pressure remained fairly constant until the last 30 minutes of the study when it tended to increase while heart rate decreased, but again no statistical difference was evident. Baseline blood pressure and heart rates were no different from those recorded during an earlier study on the same population of dogs[11].

The standard deviation of mean arterial blood pressure was 7.7–16.1 mm Hg, with exception of the 120-minute interval when it was 19.5 mm Hg. The sample size was appropriate to test the effect of diminazine aceturate on blood pressure. The power of this study was 0.916 based on the sample size of 6 and change in blood pressure of 30 mm Hg, standard

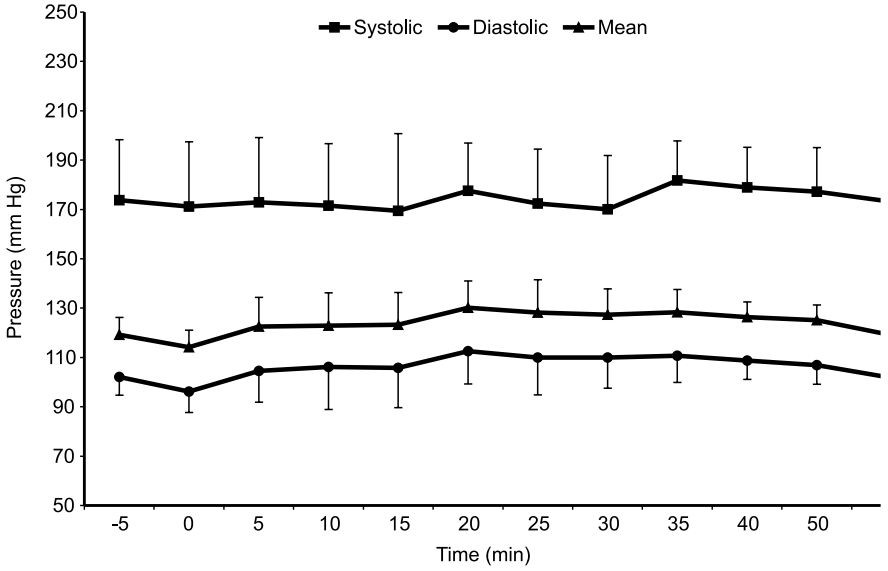

Fig 2: **Systolic, diastolic and mean blood pressure in 6 dogs after administration of diminazene aceturate. Vertical bars = 1 standard deviation, plotted only in a single direction.**

deviation of 15 and a $P < 0.05$. The power to detect a 20 mm Hg change in blood pressure was 0.743.

DISCUSSION

Hypotension has been reported to occur in both severe and complicated babesiosis prior to treatment[7,10]. Thus, any aggravation of this hypotension by treatment may induce shock in compromised patients. As diminazene aceturate has been implicated in causing hypotension, this may be a realistic threat in the treatment of patients with babesiosis. This study showed that diminazene aceturate did not induce a significant reduction ($P > 0.05$) in blood pressure following intramuscular administration in clinically healthy dogs.

The intravenous administration of diminazene aceturate has been shown to cause hypotension[8,15,18–20]. Clinically, the intravenous administration of diminazene aceturate should be avoided and the manufactures recommend only intramuscular administration. A number of reports indicate that the intramuscular administration of diminazene aceturate is not associated with hypotension[8,18]. Our results concur with these findings.

Although the sample size was small, statistically there should have been enough animals to demonstrate a decrease in mean blood pressure below 80 mm Hg (our cut off point of clinical hypotension) in this study. Our sample size was not large enough to detect a smaller decrease in blood pressure. A smaller decrease in blood pressure is unlikely to result in a significant clinical effect. The sample population may have had an influence on our results. The rise in heart rate at the 5-minute interval may have been related to intramuscular administration of diminazene aceturate and the discomfort associated with this. The catheter was flushed after a series of readings to ensure patency. The blood pressure transducer was calibrated to standard mercury column at start up and between patients and the drift was small.

The readings that were lost as result of catheter occlusion and disruption of the non-compliant tubing occurred during the 30- and 35-minute intervals. This would have occurred after the concentration of diminazene aceturate peaked before 20 minutes post-administration[12]. If any changes in blood pressure were due to peak serum concentration they would have still been evident from the results. Peak plasma concentration 20 minutes after the administration of 4.2 mg/kg diminazene aceturate was 1.69 ± 0.65 $\mu g/m\ell$* below the concentrations that have been reported to affect blood pressure by Arowola[1,2]. The duration of 120 minutes from administration allowed for more than an 80 % clearance of the drug from the central compartment[12]. All studies reporting a decrease in blood pressure following intravenous administration have reported the effect to follow the administration of diminazene aceturate and to have returned to normal with in 60 minutes[8,15,18–20]. This study should have had the sensitivity to detect these changes.

This study has indicated that diminazene aceturate with its stabiliser antipyrine has a minimal effect on blood pressure in healthy dogs. It is not evident from this study if diminazene aceturate would alter blood pressure in patients suffering from babesiosis. Babesiosis is a disease that by definition meets the criteria of sepsis[9]. A number of pathological processes are known to occur in sepsis that may influence blood pressure and shock. A study should be conducted to assess the effect of diminazene aceturate on blood pressure in clinically affected patients in relation to their normal management.

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