Arab Gulf Journal of Scientific Research, 23 (4), pp 150-157 (2005)

Review Paper Ref. No 2174

The Pharmaco-kinetics and Dose Regimens of *Aminoglycosides* in the Camel *(Camelus dromedarius)*.

الحرائك الدوائية والجرعات العلاجية لمجموعة الأمينوجلاكوسيد في الجمال.

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Abstract: In this review article pharmaco-kinetics of several *Aminoglycoside antibiotics* and their recommended doses in camel have been reviewed. The maximum and minimum inhibitory concentrations and their role in efficacy and toxicity have been discussed and correlated with that reported in other mammals. The longer half-lives of *Aminoglycoside*s in camels compared to other mammals were suggested to be related to the entire elimination of *Aminoglycosides* by glomerular filtration and the unique water conservation mechanism in camels.

Keywords: camel, camelus dromedarius, *Aminoglycoside*, pharmaco-kinetics, dose regimen, efficacy.

المستخلص: نسبة لتزايد الاهتمام بالجمال في إقليم الخليج العربي وتطور طرق رعايتها، من التقليدية المفتوحة إلى أنظمة الحظائر المغلقة، وما قد ترتب علي ذلك من تفشي الإصابة بالأمراض البكتيرية والإكثار من المعالجة بالمضادات الحيوية، إلى جانب اضطرار البيطريون، ولانعدام وجود جرعات دوائية خاصة للجمال، علي توظيف جرعات الدواء المصنعة لأنواع أخرى، مثل الأبقار والخيول، وما قد يترتب علي ذلك من أعراض جانبية ضارة في الجمال، تستهدف هذه الدراسة إعادة حساب جرعات الأمينوجلاكوسيد *Aminoglycoside* في الجمال استنادا إلي الحرائك الدوائية لها علي نظام الجرعة اليومية الواحدة، للوصول إلي تركيز المادة في مصل الدم ليصل إلي عشرة أضعاف أقل تركيز فعال، شرط التأكد من فعالية هذه الجرعات إكلينيكيا. وذلك استناداً علي دراسات عدة في أيض وحركة الدواء في الجمال، وتحديدا مجموعة الأمينوجلاكوسيد *Aminoglycoside*، لأهميتها في علاج حالات البكتيريا المستعصية، علي الرغم من سميتها علي الكلي والأذن الداخلية. تتوافق هذه الدراسة مع اهتمام العلماء طوال العقود الماضية بتغيير نظام الجرعات المتكررة للأمينوجلاكوسيد *Aminoglycoside* في اليوم الواحد لما لها من متطلبات ومعوقات، إلي نظام الجرعة الواحدة استنادا علي عدة حقائق علمية قد أثبتوا صحتها. منها أن مجموعة الأمينوجلاكوسيد *Aminoglycoside* فعالة في قتل البكتيريا، علي الرغم من تدني تركيز الدواء وأيوله إلي مستوي الصفر في الدم، مما يعني تجاهل دور تحديد أدني تركيز فعال في تحديد الجرعة الدوائية ومدى سميتها. كما أن المفعول المضاد للبكتيريا فيها يتناسب طردياً مع تركيز الدواء في الدم ، مما يعني أنه كلما كبرت النسبة ، بين أعلي تركيز وأقل تركيز فعال ، كلما زاد معدل قتل البكتيريا. إضافة إلي أن تركيز مجموعة الأمينوجلاكوسيد *Aminoglycoside* في الكلي والأذن الداخلية يصل إلي درجة التشبع عند تركيز منخفض جداً، مما يعني عدم جدوي التركيز لزيادة درجة فاعليتها. وفوق هذا وذاك، أن البكتيريا تظهر مقاومة لمجموعة الأمينوجلاكوسيد *Aminoglycoside* عند التعرض لها، ولهذا فإن تدني تركيز الدواء في الجسم وأيوله إلي مستوي الصفر ، يعني التخلص من ظاهرة مقاومة البكتيريا للدواء.

كلمات مدخلية: الجمال، حظائر مغلقة، بكتيريا، مجموعة الأمينوجلاكوسيد، حرائك دوائية، جرعات.

Introduction

Camel *(Camelus dromedarius)* is an essential domestic animal found mostly in arid and semi-arid region of the world. It is employed for many functions in nomadic societies as a source of meat, milk, hair and hides and for drought and transport. In the Arabian Gulf countries, it is also used in organized sport races. The camel is again becoming an important farm animal due to drought and desertification of large areas where sheep and cattle have been grazing. The husbandry of the camel is likely to change from pastoral to close-confinement and stall-feeding. Under these conditions, health problems associated with bacterial infections are expected, creating an increase in the use of antibacterial drugs.

In spite of the well-recognized renal and otic toxicity of *Aminoglycoside* antibiotics, (Black *et. al.*, 1976); (Moore *et. al.*, 1984); (Bennett, 1989); (Begg and Barcaly, 1995) they are still frequently used in the treatment of several infections due to their effectiveness in rapidly and almost completely eliminating of large number of gram-negative and several types of gram-positive pathogens.

Due to paucity of dose recommendation of therapeutics agents in camels, it is often assumed, without scientific basis, that the doses of therapeu-tics agents in camels are not different from that of other large domestic animals such as equine and bovine species.

Recently a considerable amount of pharmaco-kinetics research has been done in camels (Ali, 1988); (Ali and El Sheikh, 1992); (Wasfi *et. al.*, 1992; 1993; 1998; 1999); (Abdel Hadi *et. al.*, 1994, 1998) providing a scientific basis for selecting an appropriate dosage regimen rather than extrapolating data from other species, with potential adverse reactions in camels (Ali, 1988).

For greatest efficacy, an *Aminoglycoside* dosage regimen should provide drug concentration at the infection site, which optimises pharmaocdynamic action and minimises toxic effect to the host. Traditionally, *Aminoglycoside* are administered in multiple daily doses (once every 8 or 12 hours). However, clinicians worldwide are becoming increasingly aware that the standard regimen is no longer an acceptable practice. Clinical experience over (60 years) has shown that the multiple daily dosing strategies to be both labour and lab-intensive. Correct multiple daily dosing of Aminoglycosides often requires pharmaco-kinetics expertise and close monitoring of the drug serum levels and renal function. Therapeutic drug monitoring has been used extensively to guide dosage adjustments to maximize efficacy and minimize toxicity. Therefore, the potential advantages of once-daily *Aminoglycoside* dosing have received recent attention (Parker *et. al.*, 1993); (Prins *et. al.*, 1993). The rational for the once-daily dosing of *Aminoglycoside*s is based on the following obser-vations: -

(**1**). *Aminoglycosides* exhibit a significant post-antibiotic effect (PAE). (Craig and Gudnundson, 1990). The (PAE) refers to the continued suppression of bacterial growth despite the decline of ant microbial concentration to zero.

(**2**). The bacterial action of *Aminoglycoside* is concentration dependent, i.e. the higher or the peak / minimum inhibitory concentration *(MIC)* ratio the higher kill rate (Moore *et. al.*, 1984).

(**3**). Aminoglycoside is taken up into renal tubule cells and the inner ear appear to be saturated at relatively low serum levels, suggesting that higher peaks do not necessarily result in a greater risk of toxicity.

(**4**). In vitro studies on *Aminoglycoside*s show an adaptive post-exposure resistance (Karlowsky *et. al.*, 1994)

In an ideal study, the pharmaco-kinetics of free *Aminoglycoside* obtained by two or more dosage regimens should be compared in relation to sensitivities and correlated with success or failure of therapy in camels. These criteria have not been met by previously reported studies (El-Gendi *et. al.*, 1983); (Ziv *et. al.*, 1991); (Wasfi *et. al.*, 1992, 1993, 1999); (Abdel Hadi *et. al.*, 1994, 1998). This article compares, correlates and comments on the pharmaco-kinetics values and the recommended doses of *Aminoglycoside* antibiotics in normal camels with the recommended doses and their serum concentration, therapeutic efficacy and toxicity in other large animals and in vitro studies.

Drugs: Pharmaco-kinetics Values

(1)*Gentamicin*

Gentamicin has a wide antibacterial spectrum of activity against animal pathogens, especially in the treatment of severe gram-negative sepsis. Its disposition was studied in normal and water deprived camels (Wasfi *et. al.*, 1991); (Ziv *et. al.*, 1991) (Table 1). It was found that water-deprivation has no significant effect either on distribution or elimination kinetics of *Gentamicin*. Pronounced reductions were observed in both the rate and extent of absorption from the intramuscular (i.m) injection site. The maximum concentration (Cmax.), the time to maximum concentration *time to* (Tmax) and the area under the curve (AUC) were approximately (50%) in dehydrated camels. Low *Gentamicin* bioavailability (F) was attributed to decreased absorption from (i.m) injection site in dehydrated camels resulting from changes in peripheral circulation.

In the non-dehydrated camel the elimination half-life (tfi) (2.92±0.12h) reported by (Wasfi *et. al.*, 1992) is in agreement with that reported by (Ziv *et. al.*, 1991) (2.93±0.24h). The volume of distribution at steady state (Vdss) and the total (Clt) values reported by (Wasfi *et. al.*, 1992) are lower than that reported by (Ziv *et. al.*, 1991) (See, table 1). These reductions in *Gentamicin* volume of distribution at steady state value (Vdss) and *T*otal body clearance value (Clt) were attributed to the difference in the dose. It is interesting to recall here that *Gentamicin* follows dose dependent kinetics in sheep (Brown *et. al.*, 1986).

Based on the pharmaco-kinetics value of *Gentamicin* obtained from normal and dehydrated camels (See, table 1), a dose of (2 - 2.75 mg/kg) every (12 hr.) (Ziv *et. al.*, 1991); (Wasfi *et. al.*, 1992) or a dose of (3 mg /kg) as a once daily, were recommended (Wasfi *et. al.*, 1992). The suggested doses are based on the assumption that the average steady state concentration volume of distribution at steady state value (4- 4.3μg/ml) achieved with the recommended doses should be within the minimum inhibitory concentration (MIC) of *Gentamicin* reported for most susceptible organisms (3- 5μg/ml)

Table (1): Disposition kinetics of *Aminoglycoside* in Camels.

Drugs/Dose/kg	(t fi) h	(Clt) ml/kg/h	(Vdss) ml/kg	(C max) ug/ml	(Tmax) min	(F%)	References
Gentamicin	2.92±0.12	62.7±5	260.6±12.8	9.36±0.5	30±3	89.9 5.7	(Wasfi *et. al.*, 1992)*
3mg/i.m & i.v	2.93±0.24	81±6.6	21±19.4	5.4±0.4	65.1±13	54±6	(Ziv *et. al.*, 1991)**
2mg/i.m & iv							
Kanamycin	3.02±0.28	72.7±6.6	309±17.1	15.4±0.8	31.3±3.6	93.7 8.2	(Wasfi *et. al.*, 1993)*
6mg/i.m&i.v							
Tobramycin	3.15±0.35	54±6	228±21	3.32±0.59	30	90.7 14.4	(Abdel Hadi*et. al.*, 1994) **
1mg/i.m, 1.3mg/i.v							
Streptomycin	3.35	56.1	248	33.15	30	99	(Abdel Hadi *et. al.*,1998)***
10mg/i.m & i.v	8.28±0.24	-	-	7.81±0.1	84±0.	-	(El-Gendi *et. al.*,1983)*
10mg/i.m							
Amikacin	2.92	61.2	221.2	12.3	56.4	96.5	(Wasfi *et. al.*, 1999)***
3.75mg/i.m&i.v							

(tfi) = Elemination half life, calculated from (i.v. Administration)
(Clt) = Total body clearance value calculated from (i.v. Administration)
(Vdss) = Volume of distribution at steady state value calculated from (i.v. Administration)
(Cmax) = maximum concentration, calculated from (i.m. Administration)
(Tmax) = Time to maximum concentration, calculated from (i.m. Administration)
(*) = Values are mean ± S.E.M., (**) Values are mean ± S.D., (***) Values are median.

(Conzelman *et. al.*, 1980). A maximum concetration (Cmax) of (11-11.5 μg/ml) would be expected and would be less than the reported toxic concentration of *Gentamicin* (12μg/ml). (Gyselynck *et. al.*, 1971). However the reported toxic concentration of *Gentamicin* (12 μg/ml) is indistinguishable from the maximum concetration (Cmax) (11-11.5 μg/ml) in a biological system so it cannot be claimed that it is less than the reported toxic concentration of *Gentamicin*. The multiple daily doses recommended by (Ziv *et. al.*, 1991) and (Wasfi *et. al.*, 1992) were in agreement with conventional therapeutic doses reported for other animals (See table 3) (Huber, 1977); (Barragry, 1994). The recommended once daily dosing of *Gentamicin* (3mg/kg) (Wasfi *et. al.*, 1992) may be inappropriate because, it does not attain a maximum concetration (Cmax) of (10) times the minimum inhibitory concentration (MIC). Accordingly, we suggest a once daily dose of (8.5-14mg/kg) to achieve a Maximum Concetra-tion (Cmax) of (30-50 μg/ml) (>10x minimum inhibitory concentration (MIC), Minimum Concertration (Cmin.) of (0.1 0.16 μg/ml) and volume of distribution at steady state value (Cavgss) of (5 - 8 μg/ml).

(2) *Kanamycin:*

Kanamycin is an effective *Aminoglycoside* antibiotic for the treatment of a wide range of facultative gram-negative bacteria. The pharmaco-kinetics of this drug in normal camels was studied (Wasfi *et. al.*, 1993). The *Kanamycin* elimination half life (tfi) in camels' (3.02 (0.28h) (See, table 1) was found to be longer than that reported in guinea pigs, sheep, and human (See, table 3). The differences were suggested to be related to a unique water conservation mechanism in the camel (Wasfi *et. al.*, 1993). In the later study, and from the kinetics data obtained, a dose regimen of (8.5 mg/kg/12h) was suggested to achieve steady state serum concentration (Cavgass) of about (10 g/ml), with peak and trough concentrations of about (29) and (1.8 μg/ml) respectively (See, table 2). The recommended multi – daily dose of *Kanamycin* for camels is consistent with those reported in sheep goat, cattle, horse and pigs (See, table 3) (Huber, 1977); (Barragry, 1994). This multi - daily dose regimens based on the consensus view evolved that the serum concentrations should be maintained below the reported toxic and trough concentrations to minimise toxicity. The therapeutic and trough concentrations expected in camels were of the same magnitude as that reported

Table (2): Intramuscularly recommended dose of *Aminoglycoside* in camels and their expected plasma concentrations

Drugs	Dose rate	*Cmin*	*Cmax*	*Cavgss*	References
Gentamicin	2.75mg/kg/12h 2mg/kg/12h	0.6μg/ml	11μg/ml	4μg/ml	(Wasfi *et. al.*, 1992) (Ziv *et. al.*, 1991)
	8.5-14mg/kg/24h	1-0.16μg/ml	30-50μg/ml	5-8μg/ml	*
Kanamycin	8.5mg/kg/12h	1.85μg/ml	29μg/ml	10μg/ml	(Wasfi *et. al.*, 1993)
	13mg/kg/24 h	0.16μg/ml	40μg/ml	7μg/ml	*
Tobramycin	2.5/mg/kg/12h	0.5 - 1μg/ml	10μg/ml	3.5-4μg/ml	(Abdel Hadi *et. al.*, 1994)
	4mg/kg/24h	0.1μg/ml	16μg/ml	4μg/ml	*
Streptomycin	10mg/kg/8-12h	8 - 3μg/ml	45-40μg/ml	20-15μg/ml	(Abdel Hadi *et. al.*, 1998)
	12.5 - 25mg/kg/24h	0.3-0.6μg/ml	50-100μg/ml	0-20μg/ml	(Abdel Hadi *et. al.*, 1998)
Amikacin	8mg/kg/12h	2μg/ml	30μg/ml	10μg/ml	(Wasfi *et. al.*, 1999)
	10mg/kg/24h	0.2-0.3μg/ml	40μg/ml	7μg/ml	(Wasfi *et. al.*, 1999)

* *New doses recommended by the authors.*
* *Cmax = maximum concetration*
* *Cmin = minimum concertration*
* *Cavgass = Coverage steady state concentration*

in other animals and the biological fluids (Marik *et. al.*, 1991).

To achieve a high maximum concetration (Cmax), lower Minimum Concertration (Cmin.) values and longer intervals of dose administration, a dose rate of (13 mg/kg/24h) was recommended. This dose was expected to achieve a maximum concetration (Cmax) of (40 μg/ml) which is more than (10 times) the Minimum Concertration (Cmin.) of many susceptible organisms, and Minimum Concertration (Cmin.) of (0.16 μg/ml) which is lower than the reported Minimum Concertration (Cmin.) of (1 - 4 μg/ml).

(3) *Tobramycin:*

The antimicrobial activity and pharmaco-kinetics properties of *Tobramycin* are very similar to those of *Gentamicin*. (Abdel Hadi *et. al.*, 1994) studied *Tobramycin* disposition in normal camels following (i.v) and (i.m) administration (See table 1). Compared to previous work in humans, dogs and cats, the elimination half life (tfi) of *Tobramycin* in camels was (164 – 215 min) (harmonic mean 188 min), was longer. This was suggested to be related to the lower glomerular filtration rate in hydrated camels than human, dogs and cats. The glomerular filtration rate in hydrated camel has been reported to be one-haif of that in cattle (Wilson, 1984). Dependent on the kinetic values reported (See, table 1) a dose rate of (2.5mg/kg) administered by (i.m) injection at (12h) intervals was recommended (Abdel Hadi *et. al.*, 1994). The dose was expected to achieve a maximum concetration (Cmax) of (10μg/ml), trough concentration of (0.5 -1μg/ml) and volume of distribution at steady state value (Cavgss) of (4μg/ml). Based on the suggested approach to once daily dose, a dose rate of (4 mg/kg/24h) is recommended. The recommended dose would be expected to achieve an average steady serum concentration of 4 (μg/ml), maximum concetration (Cmax) of 16μg/ml) and trough concentration of (0.1μg/ml). A trough concentration less than (2 μg/ml) for *Tobramycin* and *Gentamicin* were the traditional goals of therapy, which, increase the efficacy and decrease the incidence of toxicity (Barclay *et. al.*, 1994).

(4) *Streptomycin:*

Streptomycin is a potent antibiotic. It is active against gram-negative organisms, especially mycobacterium tuberculosis, and can broaden the antibacterial spectrum of a few antimicrobial drugs that are only active against gram-positive bacteria (Sand and Mandel, 1993). Unlike other *Aminoglyco-*

Table (3): Traditional intramuscular multiple daily doses of *Aminoglycoside* antibiotics recommended in human and animals species.

Drugs	Animal Species	Doses/ i.m	References
Gentamicin	Horse, cattle, sheep and goat Pigs	2.2 - 4.4mg/kg/8 -12h 2mg/kg/8h 5mg/kg/8-12h	(Barragry, 1994). (Huber, 1977). (Barragry, 1994).
Kanamycin	Horse, cattle, sheep, goat and pigs Dogs and cats	5 - 12mg/kg/12h 5mg/kg/8h	(Huber, 1977); (Barragry, 1994). (Huber, 1977); (Barragry, 1994).
Tobramycin	Human	1 mg/kg/8h	(Barragry, 1994).
Streptomycin	Horse, cattle, sheep, goats and pigs	10 - 12mg/kg/8 - 12h	(Brander and Pugh, 1977); (Huber 1977); (Barragry, 1994).
Amikacin	Human	5 - 7.5mg/kg/8-12h	Barragry.1994.

side antibiotics, *Streptomycin* has not been so widely used alone in human and veterinary medicine, because of it's severe ototoxicity, nephrotoxicity and rapid development of resistance when used in traditionally multiple daily doses. (Barza and Scheit, 1977); (Brander and Pugh, 1977); (Huy *et. al.*, 1983). (Abdel Hadi *et. al.*, 1998) provide addition information on pharmaco-kinetics parameter of *Streptomycin* in camels (See, table 1) to that previously reported (El-Gendi *et. al*, 1983). The elimination half life (tfi) (3.35h) of *Streptomycin* in camels was similar to that obtained in others *Aminoglycoside* antibiotics in camels measured by fluorescence polarisation immunoas-say (See, table 1). In contrast, the elimination half life (tfi) (8.28 h) of *Streptomycin* in camels determined by microbiological assay was longer (El-Gendi *et. al.*, 1983). This deference may attributed to the deferent in assay methods.

Based on the pharmaco-kinetics values obtained (See, table 1) a dosage of (10 mg/kg) administered at (8 to 12h) intervals that provided a steady state serum concentration of (20 μg/ml) was recommended. A once daily dose of (12.5-25 mg/kg), which produced a maximum concetration (Cmax) of 50-100 μg/ml) and Minimum Concertration (Cmin.) of 0.3-0.6μg/ml), was also recommended. The Maximum Concentration (Cmax.) was suggested to be 10 times the minimum inhibitory concentration (MIC) (5-10 μg/ml) for most susceptible organisms isolated from other mammal (Brander and Pugh 1977); (Huber 1977); (Schwenzer and Anhalt, 1983). The therapeutic dose of *Streptomycin* in mammal approximately (12 mg/kg) intramuscularly at (12 h) intervals (Huber, 1977); (Barragry, 1994) is consistent with the recommended multi-daily dose for camels. It was concluded that the suggested *Streptomycin* dose for camels might be therapeutically appropriate.

(5) *Amikacin:*

Amikacin is a semisynthetic *Aminoglycoside* derived from *Kanamycin* with bacterial activity against a wide range of gram positive and gram-negative organisms. *Amikacin* utility is due primarily to its high degree of resistance to inactivating enzyme (Sande and Mandell, 1993). The disposition of *Amikacin* in the camel has been investigated (Wasfi *et. al.*, 1999) (See, table1). The systemic clearance of *Amikacin* in camels (0.97 ml/min/kg) was found to be lower than that reported in calves, dogs and cats but was slightly greater than that reported in sheep. (See, table 3) *Amikacin* was found to be rapidly absorbed from the (i.m) site reaching a peak concentration of (11.60 μg/ml after one hour. The systemic availability was close to (100%).

From the pharmaco-kinetics values obtained (See table 1) a suggested (i.m) dosage of (8mg/kg) injected at intervals of (12 h) was expected to give a Minimum Concertration (Cmin.) (2μg/ml), maximum concetration (Cmax) (30μg/ml) and volume of distribution at steady state value (Cavgss) of 10μg/ml) (Wasfi *et. al.*, 1999). A once-daily dose of (10 mg/kg) was also suggested (See, table 2) and would be expected to produce a maximum serum concentration *(Cmax)* of (40 μg/ml). This was found

to be (10-40) times the minimum inhibitory concentration of (1-4 μg/ml) of many susceptible organisms, and was expected to give a higher kill rate (Moore *et. al.*, 1984). A trough concentration of (0.2-0.3 μg/ml) was expected and for (5-7h) the serum concentration would be less than (0.5 μg/ml). It is known, however, that minimum inhibitory concentration (Cmin) of (0.5- 5 μg/ml) has been reported from many animal species to minimize toxicity and permit the reversal of the adaptive post exposure resistance (Karlowsky *et. al.*, 1994).

Discussion

Physiochemical properties of *Aminoglycoside* antibiotics determine their disposition behaviour in the body. It would appear from the kinetics results presented, the longer half-life and shorter systemic clearance rate of *Aminoglycoside* in camels were observed compared to those of other animals (Ziv *et. al.*, 1991); (Wasfi *et. al.*, 1992, 1993, 1999); (Abdel Hadi *et. al.*, 1994, 1998). The differences could not be explained on the basis of drug metabolising ability of the camel as the *Aminoglycoside* antibiotics are eliminated unchanged by renal glomerular filtration (Schentog, 1982). The longer half-lives of *Aminoglycosides* in camels compared to other animals were suggested to be related to the unique water conservation mechanism in the camel (Ziv *et. al.*, 1991); (Wasfi *et. al.*, 1992, 1993, 1999); (Abdel Hadi *et. al.*, 1994, 1998). For example the lower renal glomerular filtration rate in hydrated camel compared to that of the cows under similar conditions (Wilson, 1984) was though to be the cause of longer half-life of *Aminoglycoside* in camel (Wasfi *et. al.*, 1993). The small volume of distribution at steady state value (Vdss) of all *Aminoglycoside* antibiotics was expected for such polar compounds, which distributed mainly in the extra cellular fluid.

Following (i.m) administration, *Aminoglycoside* antibiotics were rapidly absorbed reaching peak concentration after (30–60min) and their absolute bioavailability were close to (100%). (Wasfi *et. al.*, 1992, 1993, 1999); (Abdel Hadi *et. al.*, 1994,1998).

The multiple doses of *Aminoglycosides* advocated for camels (See, table 2) (Ziv *et. al.*, 1991); (Wasfi *et. al.*, 1992, 1993, 1999); (Abdel Hadi *et. al.*, 1994, 1998) were within the range of the conventional doses previously reported for other large animals (See, table 3) (Brander and Pugh, 1977); (Huber, 1977); (Barragry, 1994). These conventional doses were determined by matching the pharmaco-kinetics obtained in normal animals to the activity in vitro. An attempt is made to maintain serum concentration above the minimum inhibitory concentration (MIC) for nearly the entire dosing intervals, and maximum concetration (Cmax) less than the reported toxic level. This guideline for selecting dosing regimen is based on the observations made almost (50 years) ago using penicillin to treat a few strains of *Streptococci* and *Treponema pallidum* in animal infection models (Jawetz, 1946); (Eagle *et. al.*, 1953). Recently (Vogelman *et. al.*, 1988) reported that the log area under the curve *(AUC)* was the major pharmaco-kinetics parameter-determining efficacy for *Aminoglycoside* doses. The optimal dosing intervals were no greater than the time serum level exceeded the minimum inhibitory concentration (MIC) plus the duration of the post-antibiotic effect. The post-antibiotic effect phenomenon suggests that the *Aminoglycoside* serum level may be allowed to fall bellow the minimum inhibitory concentration (MIC) of the pathogen without compromising anti-microbial efficacy. The duration of post-antibiotic effect depends on several factors; chief among them is the height of the preceding *Aminoglycoside* peak (Craig and 0Gudmundson, 1991). Serum trough level that is at or near zero may promote tissue drug disposition, shorten tissue exposure and promote recovery. Therefore, shorter exposure time to the *Aminoglycoside* appear to be safer. (Karlowsky *et. al.*, 1994) reported that more frequent dosing of *Aminoglycoside* tend to produce an adaptive post-exposure resistance phenomenon i.e. longer dosing intervals appear to shorten time required for minimum inhibitory concentration (MIC) to revert to its original value.

In addition *Aminoglycoside* exhibit concentration dependent bactericidal activity at levels above the minimum inhibitory concentration (MIC) i.e., Higher the peak / minimum inhibitory concentration (MIC) ratio the higher kill rate (Moore *et. al.*, 1984).

The multiple daily dosing usually results in relatively low peak/minimum inhibitory concentration (MIC) ratio (<5), but when the same total daily dose is given as a single bolus, much higher ratios are obtained (<10). Higher peaks of *Aminoglycoside* do not necessarily result in a great risk of toxicity, because uptake in renal tubule cells and the inner ear appear to be saturated at relatively low serum levels. In conventional multiple daily doses, the main aim of monitoring *Aminoglycoside* concentration is to avoid overdosing and potential toxicity. Toxicity has been associated with the total daily doses, (Jackson and Arcieri, 1971); (Waits *et. al.*, 1971), duration of treatment, (Waits *et. al.*, 1971); (Black *et. al.*, 1976) failure to make dose adjustment in a patients with renal insufficiency (Jackson and Arcieri, 1971), high peak or trough serum concen-

tration (Black *et. al.*, 1976); (Goodman *et. al.*, 1975) and liver disease (Moore *et. al.*, 1984).

In addition to the above cited evidences which were not determined in camels, the multi-dose response studies and the minimum inhibitory concentration (MIC) of microorganisms from isolates of camel origin which are susceptible to *Aminoglycoside* have not been determined (El-Gendi *et. al.*, 1983); (Ziv *et. al.*, 1991); (Wasfi *et. al.*, 1992, 1993, 1999); (Abdel Hadi *et. al.*, 1994, 1998). Therefore, it is difficult to choose multiple daily doses that achieve the maximum efficacy with least amount of drug and thus minimum toxicity.

New *Aminoglycoside* dosing strategies, however, have evolved recently with the aim of reducing treatment failure and drug toxicity. (Labowitz *et. al.*, 1974) was the first to introduce the once daily dosing, which has gained wider acceptance and recognition because of its ease and comparable safety and efficacy (Marik, 1991); (Tulken *et. al.*, 1991); (Barclay *et. al.*, 1994); (Begg *et. al.*, 1995); (Galloe *et. al.*, 1995); (Schumock *et. al.*, 1995). The aim of once-daily dosing is to achieve a high *Aminoglycoside* peak (>10xminimum inhibitory concentration (MIC) to maximize efficacy and to allow a drug free interval of (3 – 5h) to minimize toxicity and permit the reversal of the adaptive post-exposure resistance (Craig and Gudmundson, 1991); (Karlowsky *et. al.*, 1994); (Begg and Barclay, 1995). Practical advantages include straightforward dosage calculation; decrease personnel time; it does not required assays for therapeutic drug monitoring in short course treatment (4 – 5 days) and lower consumable cost (Parker and Davey, 1993).

According to the above rationalization for the use of pulse dosing of *Aminoglycosides*, a once – daily dose was recommended for camels. The dose should achieve a peake (10 x minimum inhibitory concentration (MIC) and trough concentration at or near zero.This recommended dosig rate, however, need, to be evaluated clinically by multiple dose study to confirm these predictions and also to determined the toxiciyt.

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Ref: 2174
Received: 05/11/2004
In Revised form: 30/10/2005