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Comparison of serum oxytetracycline concentration after intravenous and intraosseous administration in dogs

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Abstract

Intraosseous infusion is considered a useful technique for administration of medications and fluids in emergency situations when peripheral intravascular access is unsuccessful. The purpose of this study was to compare the effectiveness of intraosseous (IO) versus intravenous (IV) administration of oxytetracycline for delivery of antibiotic to the central circulation in dogs. Four intact mongrel dogs weighing 15-20 Kg of both sexes between 1 to 3 years old received 20 mg/kg oxytetracycline intravenously. The animals were allowed to recover, and, after a two-week timeout period, each dog received the same antibiotic and dose as before through a femoral Jamshidi bone marrow needle. Blood samples were taken for antibiotic assay immediately before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 24 hours after injections using high-performance liquid chromatography (HPLC). Analysis of variance revealed statistically significant differences between serum oxytetracycline levels comparing intraosseous and intravenous administration at all assay intervals. Serum levels of oxytetracycline after IV administration were significantly higher than those after IO injection at all time intervals but decreased significantly at 24 hours after injection. Peak oxytetracycline serum concentrations were achieved in IV (7.69±1.25 µg/ml) and IO (4.20±0.09 µg/ml) routs after 0.5 and 2.5 hours, respectively. However, Oxytetracycline levels were above therapeutic concentration by both intravenous and intraosseous routes. No side effects were observed in relation with the intraosseous administration of the drug. Thus, IO route appears to be practical and effective for the rapid delivery of oxytetracycline in dogs. In conclusion, oxytetracycline may be administered intraosseously when intravenous access is not possible.

Key words: Intraosseous injection, Jamshidi needle, Oxytetracycline, HPLC, Dog

Introduction

Immediate intravascular access is the mainstay of resuscitation. Traditional intravenous catheter placement may be virtually impossible in small animal neonates, especially those presenting with burns, hypovolemia, or hemorrhagic shock (Cartotto, 2009). Intraosseous infusion may have an important role as an alternative technique for establishing intravascular access and for the administration of medications and fluids in the emergency setting (Leidel et al, 2012). This clinical

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condition is commonly seen in puppies suffering from parvoviral gastroenteritis, kittens suffering from panleukopenia virus infection or animals with systemic bacterial infections. If intravenous access is not readily available for administration of fluids and antimicrobial agents, morbidity and mortality are adversely affected. Intraosseous infusion of fluids, blood products, and various drugs have shown to be very effective as an alternative to intravenous infusion (Olsen et al, 2002). For this reason, there are many studies on intraosseous injections in humans and animal models. Wood et al (2005) compared the effect of IO and IV administration of lidocaine on heart rate of twenty adult subjects. Hoskins et al (2012) compared the pharmacokinetics of intraosseous drug delivery via tibia or sternum, with central venous drug delivery during cardiopulmonary resuscitation in anesthetized swine. Chastagner et al (2001) compared serum levels achieved by equal bolus dosages of two antibiotics (amikacin and vancomycin) administered through an intratibial needle, an intraosseous implantable device and central IV routes in micropigs.

Despite the growing popularity of IO infusion for humans in emergency medicine, to date there has been little research on the IO administration of antibiotics in dogs. Only Lavy et al (1995) studied disposition kinetics of ampicillin administered intravenously and intraosseously to canine puppies. In addition, Goldstein et al (1995) administered an aqueous solution of ampicillin sodium intravenously and intraosseously to six kittens.

Tetracyclines such as oxytetracycline are effective against both aerobic and anaerobic gram-positive and gram-negative bacteria, mycoplasmas, rickettsiae, chlamydiae, as well as protozoa. Oxytetracycline is used in both dogs and cats to treat bacterial infections, including respiratory infections of the sinuses, wound infections, pneumonia, infections of the ocular and oral cavity and infections of the bone and blood cells. Also, tetracyclines are considered the drug of choice for blood cell and tick-borne infections in dogs such as Rocky Mountain spotted fever, Lyme disease, ehrlichiosis, and feline infectious anemia (hemobartonellosis). It is also used to treat conjunctivitis, particularly in cats (Maddison et al, 2008). For this reason, this drug can also be prescribed in emergencies to treat infections. It seems that no research has been done on measuring the concentration of this drug in the blood after intraosseous injection in dogs. Therefore the objective of the present study was to compare the serum concentration of intraosseous versus intravenous administration of oxytetracycline hydrochloride (OTC) in dogs.

Materials and Methods

Four adult mongrel male dogs weighing 15-20 kg of both sexes between 1 to 3 years old were used for this study. All dogs appeared healthy, as determined by results of physical examination. The dogs were housed separately in a controlled environment and fed a home-made diet containing chicken and rice. Water was available ad libitum. The animal care was done under supervision of suitably qualified veterinarian. At the first step each dog received 20 mg/kg oxytetracycline hydrochloride (Razak Pharmaceutical Co., Tehran, Iran) intravenously in cephalic vein; then, before and after 0.5, 1, 1.5, 2, 2.5, 3, 3, 5 and 24 hours after injection blood samples were taken for oxytetracycline assay. The blood samples were collected from the other cephalic veins. The animals were allowed to recover. After a two-week timeout period, each dog received the same antibiotic and dose intraosseously as before through a Jamshidi bone marrow needle after injection of local anesthesia (lidocaine) in femoral marrow cavity. Blood was centrifuged to obtain serum samples, which was stored at -80°C

until analysis by high performance liquid chromatography. Correct positioning of IO needle insertion site in all dogs was confirmed by aspiration of marrow content and easy infusion of drug as well as radiography. Levels were assayed at the same intervals and IO versus IV was compared. The dogs were followed up for a period of 4 weeks for any clinical abnormalities.

Measurement of oxytetracycline serum concentration with HPLC method

First, chromatographic standards prepared by serial dilutions (2, 20, 100, 200, 2000 and 20000 µL/ml) of pure oxytetracycline hydrochloride (Sigma-USA) were prepared in mobile phase solvent (methanol). The composition of the mobile phase consisted of 30% deionized distilled water and 70% acetonitrile (70/30 (v/v)). Based on protocol, 600 microliter mixed serum samples vortex with an equal volume (600 microliter) McIlvaine–EDTA buffer, was incubated at 30 °C for 30 min, and centrifuged at 3000×*g* for 30 min to deproteinate (Miller et al, 2007). Supernatants were evaporated, and the residue was stored at -20ºC until analysis by HPLC (Shimadzu, Japan). The dried residue was redissolved in 500 µL of the HPLC mobile phase, and then filtered through a 0.45:m filter. The filtrate (20 µL) was applied to a chromatographic system equipped with a column (C18) and a UV detector (Shimadzu, Japan). The detector was operated at a wavelength of 355 nm. All separations were carried out isocratically at a flow rate of 1 mL/min using the above-mentioned HPLC mobile phase at 37ºC. Each day before analysis of experimental samples, serial dilutions of pure OTC in methanol were analyzed by HPLC to generate a standard curve and to calibrate the system. The oxytetracycline concentration of samples was calculated based on Area Under Curve (AUC). The OTC recovery rate was 75%.

The arithmetic mean of serum oxytetracycline was compared between groups using repeated measures analysis of variance (SPSS, version 10, SPSS Inc., Chicago, IL, USA). The level of significance was set at $p \leq 0.05$.

Results

Technical difficulties were not encountered during IO needle placement. IO needle insertions were successful in all dogs. The time required to establish the bone marrow infusion lines ranged between 15 and 60 seconds.

Mean ± SD of serum concentrations of oxytetracycline in intraosseous and intravenous routes are shown in Table 1. Statistical analysis revealed significant differences between serum oxytetracycline levels comparing IO and IV administration at all assay intervals ($p<0.05$).

Table 1. Mean ± SD of serum concentration of oxytetracycline hydrochloride (µg/mL) in intraosseous and intravenous administration in dogs

Time (hr)	Intravenous injection	Intraosseous injection	P-Value
0	0±0	0±0	-
0.5	7.69±1.25	3.51±0.07	0.046
1	7.37±0.96	3.59±0.06	0.03
1.5	6.93±0.40	3.77±0.05	0.005
2	6.83±0.09	3.87±0.08	0.000
2.5	6.30±0.20	4.20±0.08	0.002
3	5.82±0.38	3.97±0.06	0.023
3.5	4.72±0.11	3.63±0.06	0.009
24	2.42±0.07	3.62±0.06	0.000

Based on table 1, serum levels of OTC after IO administration paralleled those after IV dosing but remained significantly lower at all times intervals with the exception of 24 hours post-injection that serum concentration of OTC after IO route

was significantly higher than IV route ($p<0.05$).

No local or systemic complication was observed pertaining to the IO procedure, including immediate extravasations of drug. The injection of drug caused only mild pain that disappears in less than 20 second.

Discussion

The intraosseous injection gains popularity for the infusion of medications, antibiotics, blood, and fluids particularly during situations of impossible venous access in children (Olsen et al, 2002). Unfortunately, there is a limited number of reports regarding the use of IO injections especially antibiotics in the animals including dogs. The most commonly used tetracycline in veterinary practice today is oxytetracycline (Riviere and Spoo, 2001).

Oxytetracycline levels achieved by the two routes were equivalent within 30 minutes of dosing. Thus, we have demonstrated rapid OTC delivery to the systemic circulation. Lavy et al (1995) also concluded that, in canine puppies, the IO administration of ampicillin produced serum drug concentrations nearly identical to those resulting from IV administration. Goldstein et al (1995) suggested that the disposition kinetics of ampicillin administered by the two routes were very similar. The IO route for vascular access is based on the presence of non-collapsing veins that drain the medullary sinuses in the bone marrow (Manggold et al, 2002). Fluorescein dye detected successful transfer from the femoral marrow cavity to the systemic circulation during cardiopulmonary resuscitation at the membrana nictitans five to 12 seconds after femoral IO injection in dogs (Aeschbacher and Webb, 1993).

The results of this study showed that oxytetracycline provided therapeutic plasma concentrations for a long period of time (longer than 24 hours) especially in IO procedure. It is known that a minimum inhibitory plasma concentration (MIC) of 0.5 µg/ml of OTC is generally accepted to be active against a wide range of pathogens (Escudero et al, 1994). The serum concentration of OTC after IO and IV administration was higher than the mean MIC values needed for many susceptible organisms. Moreover, the maximal concentrations were reached within 1-3 h, and therapeutic levels remained high for at least 24 hours. This indicates that OTC administered by both routes had plasma concentration in the therapeutic range. Therefore, the present study indicated that IO oxytetracycline administration was effective in dogs as well as IV route. Accordingly, the IO route is comparable in effect to the central and peripheral IV routes of drug administration for epinephrine, sodium bicarbonate, hydroxyethyl starch, calcium chloride, 50% dextrose in water, and lidocaine in normotensive, anesthetized dogs (Orlowski et al, 1990). Pollack and Penders study (1991) indicates that IO infusion of digoxin results in similar serum levels to those attained after IV administration, and may therefore afford a reliable means of initial digitalization.

Repeated measure analysis of variance revealed significant difference between IV (7.69 µg/mL) and IO (3.51 µg/mL) OTC administration at 30 minutes post-injections. Maddison et al (2008) believed that intravenously injected tetracyclines give somewhat higher levels only temporarily.

Serum levels of OTC after IO administration paralleled those after IV dosing but remained significantly lower at all times intervals with the exception of 24 hours post-injection that serum concentration of OTC after IO route was higher than IV route. Yost et al (2015) found that atropine administered by the peripheral IV route had a higher peak level and shorter time to peak effect than IO route, but the intraosseous route had a more prolonged duration of action. There may be a somewhat prolonged duration of action of various medications with IO administration

suggesting that the marrow cavity especially yellow bone marrow may act as a depot.

There are no adverse reactions in both IO and IV injections of OTC in dogs with the exception of mild pain in this study. Orlowski et al (1989) reported no significant difference in mean number of fat and bone marrow emboli per square millimeter of lung of normotensive dogs among the emergency drugs compared with controls. Regarding complications following IO access, the rate of adverse events is described low in literature. Overall, the devices are used for emergency resuscitation and should be removed within 24 hours of insertion or as soon as practical after peripheral IV access has been achieved to avoid from any side events. Also, if insertion of an IO device at a specific site has been unsuccessful, no other intraosseous insertions should be attempted at that site (Day, 2011).

To our knowledge, this was one of the first studies to assess IO administration of antibiotic in dogs. Finally, we can recommend OTC for IO administration in emergency situations, because serum levels were comparable with those following IV administration.

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Conflict of interest

The authors declare that there is no conflict of interest.

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مقایسه غلظت سرمی اکسی‌تتراسیکلین در دو روش تجویز داخل وریدی و داخل استخوانی در سگ

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چکیده

تزریق داخل استخوانی به عنوان یک تکنیک مؤثر برای تجویز داروها و مایعات در شرایط اضطراری است که امکان دسترسی به سیستم عروق محیطی ناموفق باشد. هدف از این مطالعه مقایسه اثربخشی تزریق داخل استخوانی و داخل وریدی برای انتقال اکسی تتراسیکلین به گردش خون مرکزی در سگ بود. چهار قلاده سگ عقیم نشده از نژاد مخلوط با وزن ۲۰-۱۵ کیلوگرم، از هر دو جنس و بین ۱ تا ۳ سال، ۲۰ میلی‌گرم بر کیلوگرم اکسی‌تتراسیکلین را به صورت داخل وریدی دریافت کردند. پس از یک دوره استراحت دو هفته‌ای، هر سگ همان آنتی‌بیوتیک و دوز قبلی را از طریق سوزن مغز استخوان جمشیدی در استخوان ران دریافت کرد. نمونه‌های خون بلافاصله قبل و ۰/۵، ۱، ۱/۵، ۲، ۲/۵، ۳، ۳/۵ و ۲۴ ساعت پس از تزریق برای سنجش آنتی‌بیوتیک با استفاده از روش کروماتوگرافی مایع با کارایی بالا گرفته شد. آزمون آنالیز واریانس تفاوت آماری معنی‌داری را بین سطوح سرمی اکسی‌تتراسیکلین تزریق داخل استخوانی در مقایسه با داخل وریدی در تمامی زمان‌های سنجش نشان داد. سطوح سرمی اکسی‌تتراسیکلین پس از تزریق داخل وریدی در تمام فواصل زمانی به طور قابل توجهی بالاتر از تزریق داخل استخوانی بود، اما به طور قابل توجهی در ۲۴ ساعت پس از تزریق کاهش یافت. حداکثر غلظت سرمی اکسی‌تتراسیکلین به ترتیب در روش‌های داخل وریدی (۱/۲۵±۷/۶۹ میکروگرم بر میلی‌لیتر) و داخل استخوانی (۰/۰۹±۴/۲۰ میکروگرم بر میلی‌لیتر) پس از ۰/۵ و ۲/۵ ساعت به دست آمد. با این حال، سطوح اکسی‌تتراسیکلین در هر دو روش تزریق داخل وریدی و داخل استخوانی بالاتر از غلظت درمانی آن بود. هیچ‌گونه عوارض جانبی مربوط به تجویز داخل استخوانی دارو در سگ‌ها مشاهده نشد. بنابراین، به نظر می‌رسد روش تزریق داخل استخوانی برای حمل سریع اکسی تتراسایکلین در سگ‌ها کاربردی و مؤثر است.

کلمات کلیدی: تزریق داخل استخوانی، سوزن جمشیدی، اکسی‌تتراسیکلین، کروماتوگرافی مایع با کارایی بالا، سگ

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