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CONCENTRATIONS OF SOME ANTIBIOTICS IN RABBITS PLASMA, GINGIVA, JAW BONE AND SALIVARY GLANDS*

BY

A. RAMADAN*, NEHAL A. AFIFI*, T. ABBAS** and A.F. EMARA**

* Department of Pharmacology, Faculty of Veterinary Medicine, Cairo University.
**Department of Oral Surgery, Faculty of Oral and Dental Medicine, Cairo University.

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SUMMARY

Single doses of ampicillin (oral and i.v.), cefotaxime (i.m. and i.v.) and clindamycin (oral and i.v.) were administered to rabbits for the determination of the concentrations of the drugs in the plasma and oral and paraoral tissues. The highest concentration of the drugs was found in the sublingual gland (for ampicillin and cefotaxime) and maxillary bone (for clindamycin) following their oral, i.m. and oral administration, respectively and in sublingual gland following i.v. injection of the three antibiotics tested. The mean peak concentrations in tissues and plasma was at about 2 hours, following administration of ampicillin, cefotaxime and clindamycin. The overall distributions in oral and paraoral tissues of the 3 antibiotics were as follows: Clindamycin > cefotaxime > ampicillin.

INTRODUCTION

The choice of the antibiotics to treat oral and paraoral tissue infections is made according to the symptoms and the susceptibility of the causative organism and the degree of penetration of these antibiotics into affected tissues. Large differences exist in the ability of antibiotics to penetrate tissues (Akimoto et al., 1983). Few studies have been carried out to determine concentrations of an administered antibiotic in human oral tissues and jaw bones (Bystedt et al., 1978, Akimoto et al., 1982, 1983) but there are no such studies in rabbits. The present investigation was undertaken to determine the concentrations of ampicillin, cefotaxime and clindamycin in the blood, gum, salivary glands, mandibular and maxillary bones of rabbits at their therapeutic doses.

MATERIAL AND METHODS

Drugs:

Ampicillin (Amphiben®, Misr Company for Pharmaceutical Industries, Mataria, Cairo Egypt), Cefotaxime sodium (Claforan®, Hoechst, Cairo, Egypt) and Clindamycin (Dalacin-C® Memphis Chemical Company, Cairo Egypt) were used.

Animals:

Two hundred and ten clinically healthy rabbits (Bosket breed), weighing from 2.00 to 2.25kg, were parched two weeks before the experiment began. During the acclimation and subsequent treatment period, food and water were provided *ad libitum*.

Grouping of Rabbits and Drug Administraton:

The rabbits were allocated into six groups of 35 animals each. The first, second and third groups were administered ampicillin orally, cefotaxime i.m. and clindamycin orally in single doses of 25, 50 and 16 mg/kg body weight, respectively. Rabbits of the fourth, fifth and sixth groups were injected intravenously with single doses of ampicillin, cefotaxime and clindamycin at the same dose rates of the first three gorups.

This research has been carried out at the Faculty of Vet. Med., Cairo University, Department of Pharmacology.

Specimens

Five rabbits from each group were slaughtered at 0.5, 2, 4, 6, 8, 12 and 24 hours post-administration. Blood and tissue specimens (parotid gland, mandibular gland, sublingual gland, gum, mandibular bone and maxillary bone) were collected from each of the rabbits. Blood was collecte in clean centrifuge tubes containing heparin and centrifuged at 3000 rpm for 15 minutes to separate plasma. All tissue specimens were washed in physiological saline for approximately 3 seconds to remove associated blood and blotted dry with filter paper before homogenizaiton. Gum and salivary glands were cut into small pieces. After washing, 4 parts (4 ml) of 1% phosphate buffer, pH 6.0 were added to 1g of tissue. The mandibular and maxillary bones were dissected free from soft tissue, washed in physiological saline to remove the blood and ground into small fine pieces. After weighing, 5 parts (5 ml) of 1% phosphate buffer were added to 1 g of tissue. All specimens were homogenized and the resulting mixtures were stored at 4°C for 18 hours to extract the respective antibiotic, then centrifuged at 1500 rpm for 15 minutes. This method was carried out as described by Akimoto et al. (1982). The plasma and resulting supernatants were assaye to determine the concentrations of antibiotic.

Analytical method:

Ampicillin, cefotaxime and clindamycin concentrations in the collected blood and tissue samples were estimated by microbiological assay technique described after Bennett et al. (1966) using *Micrococcus luteus* (ATCC 9341) for ampicillin and clindamycin and *Staphylococcu aureus* (ATCC 29737) for cefotaxime as he test organisms. Standard blanks from tissue and bone samples were prepared.

RESULTS

Following a single oral adminisration of ampicillin (25mg/kg. b.wt.), the plasma level concentration after 15 minutes was detected (2.766ug/ml) and continued to increase thereafter to reach its maximum concentration (10.168 ug/ml) after 3 hours. No amount could be detected 24 hours following ampicillin administration (Table 1). The mean ampicillin concentration in plasma following a single i.v. injection was 96.849 ug/ml after 15 minutes. This value decreased gradulally till reached its minimum concentration (0.372 ug/ml) after 12 hours post-injection.

Cefotaxime concentration in plasma after a single

Table (1): Concentrations of ampicillin, cefotaxime and clindamycin in plasma (µg/ml) of rabbits after a single oral, intramuscular and intravenous administration (X ± S.E., n=5).

Time after administration	Ampicillin concentrations (µg/ml) after single		Cefotaxime concentrations (µg/ml) after single		Clindamycin concentrations (µg/ml) after single	
	Oral administration	Intravenous injection	Intra muscular injection	Intravenous injection	Oral administration	Intravenous injection
15 min	2.766±0.016	96.849±0.525	23.404±0.036	95.228±0.093	0.520±0.014	21.520±0.014
30 min.	3.663±0.011	74.406±0.331	29.620±0.078	72.538±0.045	0.828±0.006	10.933±0.019
45 min.	4.263±0.031	57.121±0.635	34.542±0.036	52.602±0.067	1.428±0.023	2.251±0.026
1 hr.	5.012±0.036	42.494±0.934	39.598±0.030	40.748±0.086	2.217±0.020	0.947±0.015
1.5 hr.	6.502±0.018	26.385±0.432	28.674±0.066	22.504±0.008	1.803±0.014	0.750±0.012
2 hr.	8.023±0.034	20.914±0.512	20.468±0.021	13.286±0.021	1.383±0.016	0.608±0.009
3 hr.	10.168±0.041	13.610±0.354	10.466±0.049	6.368±0.023	0.880±0.006	0.556±0.005
4 hr.	7.196±0.042	8.948±0.275	4.494±0.049	2.654±0.039	0.564±0.007	0.529±0.008
5 hr.	4.754±0.022	6.110±0.200	2.208±0.012	1.144±0.004	0.360±0.007	0.424±0.004
6 hr.	3.016±0.032	3.922±0.130	0.904±0.005	0.530±0.010	0.223±0.003	0.329±0.003
7 hr.	2.026±0.018	2.818±0.107	0.438±0.008	0.222±0.007	0.147±0.002	0.261±0.002
8hr.	1.215±0.009	1.815±0.089	0.202±0.004	--	--	0.206±0.002
12 hr.	0.312±0.020	0.372±0.013	--	--	--	--

- = Non-detectable

I.M. injection (50 mg/kg b..wt.) was 23.404 ug/ml at 15 minutes and tended to increase to its maximum concentration (39.598 ug/ml) an hour post-injection. Then started to decreased gradually till it reached its lowest detectable level (0.202 ug/ml) at 8 hours, (Table 1). Following a single i.v. injection of cefotaxime, the plasma level was 95.228 ug/ml after 15 minute then decreased gradually to reach its minimum concentration (0.222 ug/ml) after 7 hours post-injection.

The clindamycin concentration in plasma after a single oral administration was 0.52 ug/ml after 15 minutes and its maximum concentration was 2.217 ug/ml at 1 hour. The drug concentration decreased gradually to the lowest detectable level (0.147 ug/ml) after 7 hours post-administration. The mean clindamycin concentration in plasma following a single i.v. injection was 21.66 ug/ml after 15 minutes. This highest level tended to decrease gradually till reached its minimum concentration (0.206 ug/ml) after 8 hours post-injection.

The mean ampicillin concentration ratios of the oral and paraoral tissues to their plasma concentrations (after a single oral and i.v. administration) are presented in Fig. 1. The highest concentration of ampicillin was found in the sublingual gland. And maxillary bone the peak mean concentrations of ampicillin in different oral and paraoral tissues were reached at 2 hours following oral administration. The mean concentration ratio of parotid, mandibular, sublingual glands, gum, mandibular and maxillary bones to their plasma concentraitons at the time of peak tissue concenttration following oral administration were 0.442, 0.541, 0.54, 0.536, 0.229 and 0.267, respectively. Ampicillin was not detected in oral and paraoral rabbit's tissues 24 hours after single i.v. injection.

The mean cefotaxime concentration ratio of the oral and paraoral tissue to their plasma concentrations after a single i.m. and i.v. injection are presented in Fig. 2. The highest concentrations of cefotaxime were found in sublingual gland. The peak mean concentrations in different oral and paraoral tissues were reached at 2 hours following i.m. injection of cefotaxime. Cefotaxime was not detected in any oral or paraoral tissues from rabbits 8 hours after a single i.v. injection.

The mean clindamycin concentration ratio of the oral and paraoral tissues to their plasma concentration after a single oral and i.v. administration are presented in Fig. 3 The highest concentrations of clindamycin were found in the maxillary bone (1.83 ug/g), parotid gland (1.343 ug/g) and mandibular gland (0.90 ug/g) at 2 hours after oral administration. Clindamycin was detected only in gum, mandibular and maxillary bones for up to 6 hours after i.v. injection, and for up to 4 hours in the parotid, mandibular and sublingual glands.

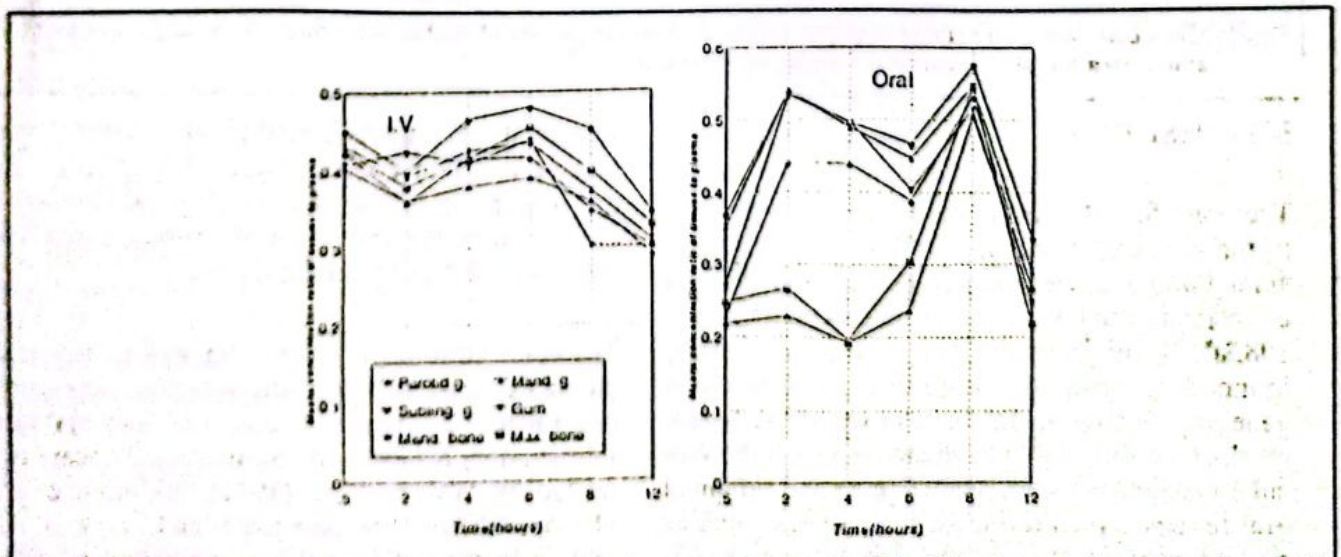

Fig. 1: Mean concentration ratio of oral and paraoral tissues to plasma of rabbits following a both single oral and I.V. administration of ampicillin (25 mg/kg boody weight).

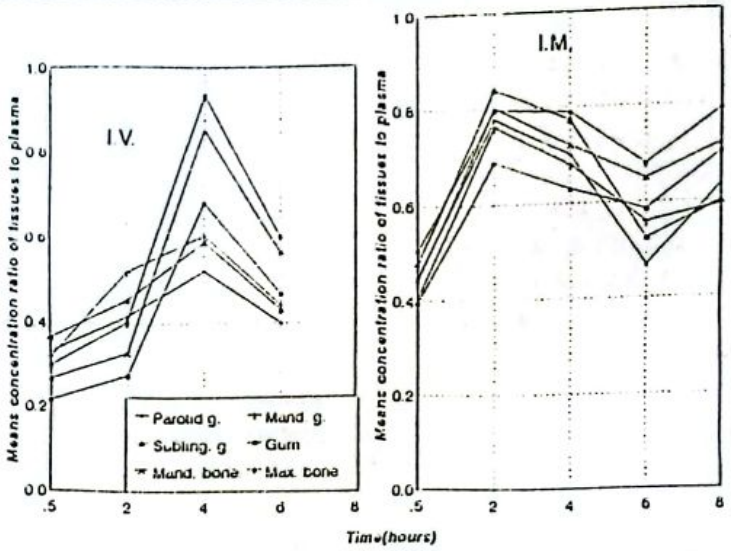

Fig. 2: Mean concentration ratio of oral and paraoral tissues to plasma of rabbits following a both single oral and I.V. administration of cefotaxime (50 mg/kg body weight).

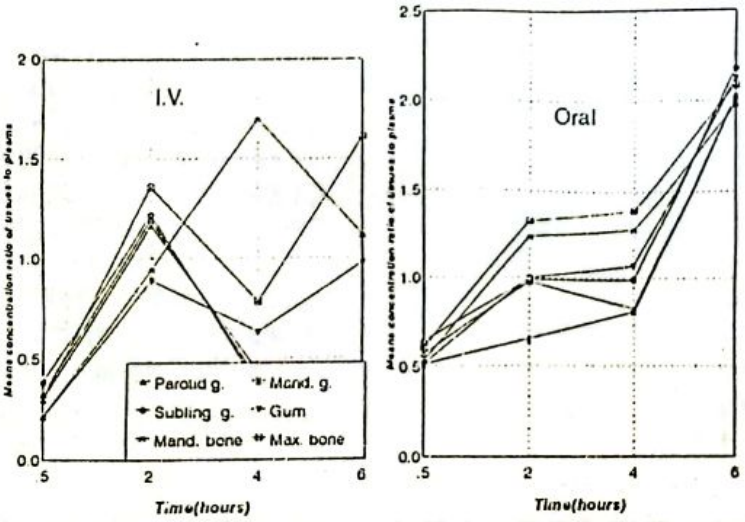

Fig. 3: Mean concentration ratio of oral and paraoral tissues to plasma of rabbits following a both single oral and I.V. administration of cefotaxime (16 mg/kg body weight).

DISCUSSION

There are few studies on the time-course changes in the concentrations of antibiotics in human or animal oral and paraoral tissues after a single oral or intramuscular administration (Akimoto et al., 1985a). In this respect, Akimoto et al., (1982), found that, antibiotic concentration in tissue is generally related to the vascularity of the tissue. Hock and Nuki (1971) have also reported the vascular changes between noninflamed and inflamed oral tissues. Since inflamed oral tissues, such as pericoronitis or chronic gingivitis, have greater vascularity than noninflamed gingiva, these tissue receive a higher concentration of ampicillin. In the present study, normal healthy rabbits were used to show the variations of antibiotic concentrations in oral and paraoral tissues.

The concentrations of ampicillin, cefotaxime and clindamycin peaked at nearly identical times, approximately 2 hours after oral, i.m. and oral administration, respectively. Similar results were reported by Walker et al. (1981), Akimoto et al. (1985a; 1985b; 1986 and 1990) and Frank et al. (1990) in man after oral administration of clin-

damycin, ampicillin and ampicillin derivatives. Highest tissue to plasma ratios of mean peak drug concentration was found in the sublingual gland after a single oral and i.m. administration of ampicillin and cefotaxime. The poor tissue distribution for ampicillin and cefotaxime in the present study as compared with clindamycin could be due to the poor lipid solubility, relatively low pka and volume of distribution (V_d) of these drugs. These results were consistent with those previously reported by Akimoto et al., (1985a, 1985b and 1986), Wildfeuer et al., (1991) and Ramadan et al., (in press) after a single oral administration of ampicillin and its derivatives. On the other hand, the highest tissue clindamycin concentration following a single oral dose was present in the maxillary bone (1.83 ug/g). Similar results were reported by Brown et al. (1990) and Budsberg et al. (1991) in cats and dogs. The bone to plasma drug concentrations ratio for the 3 tested drugs of the maxillary bone was slightly higher than that in the mandibular bone. Similar results were reported by Akimoto et al. (1982) in man after oral administration of amoxicillin. Oikarinen and Malmstrom (1972) also reported a difference of antibiotic concentration in the alveolar serum between the maxilla and mandible. The buccal and labial surfaces of the maxillary bone in the region conrresponding to the teeth apexes have more porosity than similar surfaces of the mandibular bone. This could explain why the maxillary bone showed a higher concentration of the tested drugs. Bystedt et al. (1978) reported equal peak concentration times of clindamycin, in human mandibular bone and serum following a single oral administration. There are other factors leading to a wide individual variation of antibiotic concentration in the bone. Hansen et al. (1975) and kolczun et al. (1974) reported that the antibiotic concentration in spongy bone was higher than in cortical bone following both oral and i.v. administrations. Their results indicated that bone tissue should be separated into spongy and cortical bone for the determination of antibiotic levels. In the present study, the specimens of bone were not divided.

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