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Original Article

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Quinolone levels in serum and maxillofacial tissues under ibuprofen co-administration following surgical trauma

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Abstract

Administration of antibiotics is considered to be an important factor, during or after operational procedures in the maxillofacial area, in order to avoid post-surgical complications. Furthermore, administration of anti-inflammatory drugs is often prescribed for control of the post-operative pain. The aim of this study was to determine the levels of quinolones in serum and tissues (parotid gland, tongue, mandible), during traumatic injury in the oral cavity, with or without co-administration of ibuprofen, a non-steroidal anti-inflammatory drug. Four groups of Wistar rats, (A, B control), (C, D experimental) were used. In the experimental group, traumatic injury was performed through the whole length of the cheek. Groups B and D received ibuprofen. The quinolone levels in serum and tissues were estimated by the inhibition zone of B. subtilis. Free fatty acid (FFA) levels and the adrenal weight, considered as a stress index, were increased in trauma groups. Quinolone concentrations in serum and in most of the tissues were significantly higher in the experimental groups compared to the controls. However, the co-administration of ibuprofen caused a higher increase of the quinolone levels in the control animals than in the experimental groups.

Keywords: Quinolones, Trauma, Free Fatty Acids, Serum, Ibuprofen

Introduction

The patients under surgical procedures or trauma may need drug treatment for the management of pain and infection. After surgery, many factors can alter the distribution of drugs in tissues and eventually they may affect their interactions either during metabolism or excretion[1].

Surgical operation and trauma are considered as stress stimuli altering the pharmacokinetic properties of drugs following modifications of the physiological functions of the organism. Injury-induced stress influences the levels of catecholamines, free fatty acids (FFA), corticosteroids etc. in order for the organism to be adapted[2]. The bioavailability of drugs is thus affected by the new situation, while decreased blood flow and protein, increased drug metabolizing enzyme activity and impairment of renal blood flow have been reported[3-5].

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During recent years, clinical studies showed oral quinolones to have some interesting pharmacokinetic characteristics that may explain why these drugs are sometimes more effective than, for example, oral cephalosporins[6,7]. Drugs like quinolones (ciprofloxacin, pefloxacin, norfloxacin and ofloxacin) penetrate the tissues and cells very rapidly after administration and often they achieve tissue concentrations that are several times higher than the concurrent serum levels, so they are indicated for craniofacial infections. Adverse reactions are rare and when they occur they are usually mild[8].

Co-administration of antibiotics and anti-inflammatory drugs is common during clinical practice in craniofacial disorders. In addition, anti-inflammatory drugs show a great binding ability to the proteins (serum albumin and tissue proteins) and probably they play an antagonistic role to the binding of antibiotics, since they may have a mutual binding position[9,10]. Thus, it is necessary to examine the possible interactions and the role of each drug in this respect.

The aim of the study was to investigate the fluctuations of quinolone levels, when the commonly used non-steroidal anti-inflammatory drug (NSAID) ibuprofen is co-administered under stress conditions.

Control		Trauma-stressed animals	
A	**B**	**C**	**D**
Ciprofloxacin 500mg per 12h	Ciprofloxacin + ibuprofen	Ciprofloxacin	Ciprofloxacin + ibuprofen
Pefloxacin 400mg per 12h	Pefloxacin + ibuprofen	Pefloxacin	Pefloxacin + ibuprofen
Norfloxacin 400mg per 12h	Norfloxacin + ibuprofen	Norfloxacin	Norfloxacin + ibuprofen
Ofloxacin 200mg per 12h	Ofloxacin + ibuprofen	Ofloxacin	Ofloxacin + ibuprofen
Cinoxacin 500mg per 12h	Cinoxacin + ibuprofen	Cinoxacin	Cinoxacin + ibuprofen
Ibuprofen 400mg per 12h	Ibuprofen		
Ciprocin® Bayer, Peflacine® Rhone Poulenc, Norocin® Vianex, Ofloxacin® Hoechst, Cinobactin® Eli Lilly, Brufen® Pharmalex			

Table 1. Drug dosage in the control and stressed groups.

Materials and methods

Four groups of Wistar rats (A, B, C, D) of average weight 200 g, consisting of 8 animals each were used. A and B were the control groups while the animals of group C and D were submitted to experimental trauma through the whole length of the cheek with extension to the mandible bone. Tissue trauma was performed with a lancet and was followed by an osteotomy. The animals received the drugs as indicated in Table 1.

The administration of drugs was performed in 5 oral doses, a dose every 12 hours using a special trans-esophageal catheter, following the operational procedure, meaning that duration of the experiment was 62.5 hours. The animals were sacrificed by decapitation 2.5 hours after the last dose and blood was collected from the carotid vessel. In addition, the parotid gland, the tongue and the mandible were isolated under aseptic conditions and were incubated in 2 ml sterile saline (NaCl $9^{o}/_{oo}$) at 4°C for 24 hours. The mandible was clarified from adhering soft tissues under aseptic conditions and was incubated intact.

The antibiotic levels were measured in serum and in the incubation medium of the tissues. The incubation medium was hemoglobulin free as was assessed from the N-multistix SG.Bayer index. The tissue drug level represents the capacity of each tissue to be diffused via the blood flow[1]. Drug concentrations were detected by the Bennet method in agar (Mueller Hinton Oxoid) *in vitro* by estimating the inhibition zone of B. subtilis[11]. In parallel, the FFA levels, estimated by a spectrophotometric method (Wacker-Chemie, Germany; cat.No 991-22309) and the adrenal weight were used as stress index.

Statistical analysis

Statistical differences in quinolone concentrations between controls and the experimental groups were evaluated by Student's unpaired t-test and $p<0.05$ was considered significant. In addition, the non-parametrical Anova and Wilcoxon-Mann-Witney methods were also used for unpaired values, as with t-test, in cases that the SD was significantly different from the mean values. The same methods were used for estimating the adrenal weights and coefficient correlation for evaluating the possible relationship between the changes of drug concentration and FFA levels.

Results

Ciprofloxacin

Ibuprofen treatment demonstrated a significant increase in ciprofloxacin concentrations in the mandible and the tongue as compared to control group A. Once more, the previous differences remained at mandible concentrations but were abolished for tongue concentrations as trauma and ciprofloxacin co-administration took place. Furthermore, operational procedure (group C) led to a significant enhancement of ciprofloxacin levels in both the mandible and the tongue as opposed to group A.

Pefloxacin

The pefloxacin levels in serum tended to increase in the animals under traumatic stress (C) as compared to control group A. The administration of ibuprofen alone decreased the concentrations of pefloxacin in the jawbone as compared to group A ($p<0.01$); this result did not alter despite the influence of trauma and ciprofloxacin co-administration.

Norfloxacin

In the case of norfloxacin, norfloxacin concentrations in

Ciprofloxacin				
	A control	**B control**	**C stressed**	**D stressed**
Serum μg/ml	1.06±1.3	2.03±1.94	1.65±0.99	9.65±8.6
Parotid μg/g	11.81±9.35	86.32±14.8	3.65±0.95	12.3±8.4
Tongue μg/g	2.49±1.6**(A/B)	49.74±7.36	92.2±102.8**(A/C)	23.1±4.9
Mandible μg/g	0.58±0.31**(A/B)	55.8±36.6*(B/D)	17.43±40.65*(A/C)	20.7±3.6
Pefloxacin				
	A control	**B control**	**C stressed**	**D stressed**
Serum μg/ml	0.33±0.04	5.16±4.88	0.46±0.23*(A/C)	0.87±0.6
Parotid μg/g	22.2±49.7	18.9±3.29	40.96±77.91	22.2±1.6
Tongue μg/g	4.41±4.79	3.09±2.5	3.39±3.32	11.59±18.68
Mandible μg/g	0.92±0.22**(A/B)	0.54±0.09	0.81±0.26	0.5±0.05*(A/D)
Norfloxacin				
	A control	**B control**	**C stressed**	**D stressed**
Serum μg/ml	54.03±5.15	54.74±8.09	71.06±14.8	70.2±15.11
Parotid μg/g	458.66±236.17	66.99±10.8	573.8±20.3	1087.7±63.4**(D/A)
Tongue μg/g	129.14±29.63	123.18±31.7	137.38±70.12	316.3±53.49**(D/A)
Mandible μg/g	76.6±10.75	91.59±12.1*(B/D)	78.18±10.4	102±5.4*(D/A)
Ofloxacin				
	A control	**B control**	**C stressed**	**D stressed**
Serum μg/ml	3.58±3.13*(A/B)	6.1±3.3	0.5±0.27**(A/C)	9.88±7.2**(C/D),*(D/A)
Parotid μg/g	53.4±23.69*(A/B)	26.45±12.32	15.1±13.3**(A/C)	11.34±4.15
Tongue μg/g	6.95±4.9*(A/B)	2.78±2.9	4.68±4.5	2.97±2.19
Mandible μg/g	23.5±1.7***(A/B)	3.26±2.5	2.08±0.63***(A/C)	12.11±9.4
Cinoxacin				
	A control	**B control**	**C stressed**	**D stressed**
Serum μg/ml	1.7±0.7*(A/B)	18.65±15.61	40.14±17.03***(A/C)	6.85±4.24***(C/D)
Parotid μg/g	58.54±48.2**(A/B)	179.7±40.3	110.81±90.16	92.01±34.34
Tongue μg/g	24.62±31.63	49.73±36.23	19.83±10.22	38.3±27.2
Mandible μg/g	48.23±58.15*(A/B)	7±6.17*(B/D)	44.08±26.35	13.9±6.6*(C/D),(A/B")
Values were expressed as mean ± SD *p<0.05 , **p<0.01, ***p<0.001				

Table 2. Quinolone concentrations in serum and tissues.

the parotid and the tongue increased in group D ($p<0.01$) as compared to group A, whereas in the jawbone only a minor enhancement was observed ($p<0.05$). In addition, ibuprofen treatment alone (B) resulted in significant elevation of norfloxacin concentrations in the mandible as related to group D.

Ofloxacin

In contrast to other quinolones, in goup C the observed values in ofloxacin concentrations in the mandible, parotid and serum but not in the tongue were significantly decreased

	Control animals	Stressed animals
FFA(meq/l)	0.314±0.09	0.952±0.3***
Adrenal weight (μg/g)	20.06±2.53	30.45±3.17**

Values were expressed as mean ± SD
p<0.01;*p<0.001

Table 3. Mean values of FFA concentrations in serum and adrenals' weight.

under the influence of trauma as compared to group A. In contrast, the combination of trauma and drug treatment (trauma + ibuprofen) significantly augmented the levels of ofloxacin in serum as compared to group C and A, respectively. Concerning ibuprofen administration, ofloxacin concentrations in the mandible, tongue and the parotid were significantly decreased, while in serum they were significantly increased as compared to group A.

Cinoxacin

Ibuprofen treatment (B) significantly increased the concentrations of cinoxacin in the tongue and the parotid as related to group A. In contrast, mandible concentrations of cinoxacin decreased after ibuprofen administration, as compared to group A ($p<0.05$). The co-administration of ibuprofen and cinoxacin in the case of trauma (D) tended to decrease the levels of cinoxacin in the mandible; these concentrations remained lower in relation to group C and A ($p<0.05$). Furthermore, the cinoxacin levels in serum, but not in other tissues, were enhanced under the influence of trauma (C) as compared to group A ($p<0.001$).

The FFA concentrations in serum showed statistical increases under the influence of trauma ($p<0.0001$). Similarly the adrenal weight of the experimental group was statistically significantly increased and a marked correlation between the changes in quinolone levels and adrenal weight was found under the influence of trauma, as it is described in Table 3.

Discussion

The results showed that trauma must be considered as a significant condition of stress. The increase of the adrenal weight under trauma may be due to a proliferation of the adrenal (cortex and medulla) producing hormones that influence the metabolism of the drugs by the liver[12]. This hormonal response to stress, characterized by the secretion of the "counter regulatory" hormones epinephrine, glucagon and cortisol, may satisfactorily explain the stress-induced elimination of drugs[13,14]. It is known that acidic drugs are transported from the site of administration to receptor site by plasma proteins. Serum albumin expresses a molecule with specific structure and with reactive groups that permit binding of many structurally diverse molecules. Particularly, since albumin exhibits a high affinity to acidic drugs, it has several conformation and binding sites for different drugs and molecules. In addition, corticosteroids and other agents such as endogenous substances or drugs have binding sites to serum albumin. Stress induces the enhancement of their levels, which leads to occupation of more binding sites on plasma proteins[15,16].

Trauma interferes with protein binding probably by increasing FFA[3]. This may explain the high quinolone concentration. This hypothesis cannot completely explain the increased levels, since high concentration of the drug leads to high renal excretion and consequently to decreases of the total amount of drug (bound and unbound) in the body.

Another possible hypothesis is that the competition between quinolones and FFA during renal excretion may delay the elimination of drugs from the organism. It is envisaged that organic acids are carried across the tubular cell (in active tubular secretion) by a carrier, which liberates the drug into the tubuli and returns to carry them again. The existence of the carrier has been indicated by the fact that provenecid impaired the excretion of penicillin from the kidney, leading to higher plasma penicillin concentration[17,18]. In a previous study, we have suggested that a similar mechanism, being responsible for the increase of quinolones in the presence of elevated serum FFAs, may be in operation[19].

In parallel, renal excretion may be limited by stress, since stress is accompanied by high blood viscosity[20], and possibly the observed increases of quinolone may not reflect the real situation[20]. Furthermore, in traumatized eyes of rabbits, an enhancement of elimination half-life of ciprofloxacin was observed when compared to the controls[21].

The presence of ibuprofen may potentiate quinolone displacement and consequently the observed diminution of quinolone levels may be attributed to a more active turnover of binding-displacement-excretion. Trauma, being a stress stimulus, interferes with protein binding, it alters the liver blood flow and produces changes in the microsomal enzyme activity[22-24].

Rauckman et al.[25] showed that experimental ischemic injury in rats causes a significant decrease in the activity of two major hepatic microsomal drug oxidizing enzyme systems, cytochrome P-450 and FAD (Flavin Adenine Dinucleotide) containing monooxydase. In addition, the

same group investigated the effect of trauma on sulfation and N-acetylation, major pathways of the phase II conjugation reactions of hepatic drug metabolism resulting in an enhancement or an inhibition of the enzyme activity[25]. Since norfloxacin, pefloxacin and ofloxacin are metabolized by this system, their enhanced levels during trauma may be attributed to a decreased rate of their metabolism. This may be interesting for clinical practice and it could be attributed to their distribution volume, which is more pronounced than for the rest of the agents[26,27]. It is interesting to note that trauma results in enzyme activity de-arrangement and co-substrate availability, which need special attention.

It should be noted that interactions of quinolones and ibuprofen or other propionic acid derivatives may lead to manifestations from the CNS[28,29], since it is known that arylalkanoic anti-inflammatory drugs like indomethacin/ibuprofen potentiate the antagonistic effect of quinolones to GABA, enhancing the possibility of occurrence of epileptic seizures[30].

The inclusion of ibuprofen into the therapeutic schema may also inhibit the synthesis of PGs and induce haemodynamic changes and fluctuations to the kinetics of various substances. Ibuprofen influences the kidney blood flow and consequently the kidney excretion capacity[31].

Summarizing the ibuprofen effect, two actions can be distinguished: 1) Displacement of quinolones from their binding site and 2) Impairment of renal excretion through the decreased blood flow. Furthermore, it is suggested that quinolones inhibit the p-aminohippurate transport (PAH) system across the renal tibuli[32], while ibuprofen affects the same system[33]. In response to these mechanisms, accumulation of quinolones is observed in serum and tissues. Therefore, upon co-administration with ibuprofen, quinolone levels are increased in control animals, more pronounced in serum, whereas this enhancement is less evident under stress.

The data presented in this study indicate that ibuprofen enhances the quinolone levels in the mandible, thus rendering the co-administration of ibuprofen and quinolones useful for the treatment of bone infections, since previous data have indicated that increased concentration of quinolones in the bone results in an increased clinical response of the patients treated with quinolones[34].

In conclusion, adjustment of drug dosage in traumatized, stressed patients should be taken into serious consideration, since higher levels of the quinolones are obtained under the co-administration of ibuprofen, rendering the control of the infection in craniofacial area more effective. On the other hand, an abundance of quinolones, in some cases, may result in toxic events, e.g., seizures from the central nervous system[30].

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