

Effects of early indomethacin on the lipid peroxidation in experimental spinal cord trauma

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Objective This study is planned considering the contemporary clinical and experimental investigations on the mechanisms and agents effective in the etiopathogenesis of spinal cord trauma. Unfortunately continuing insufficiencies in the management of spinal cord trauma give a great importance to experimental studies on this topic.

Methods In this study, eighty Albino-Wistar rats, divided in two groups of forty each were used. (A=control B=application). A T5-T10 total laminectomy was performed in every rat with the operation microscope and spinal trauma was achieved with an epidural cerebral aneurysm clip. Immediately on opening the clip, 3 mg/kg intraperitoneal indomethacin was given to rats in application group.

The two main groups were divided to subgroups of eight rats. It was planned to stop the biochemical

reactions at a different time in each of these subgroups, by the application of liquid nitrogen to the spinal cord and paravertebral structures at the end of minutes 1, 15, 30, 60, and 90, all the spinal cords were removed and protected from further reactions by immersion in the liquid nitrogen tank. The lipid peroxidation levels were assessed by determining thiobarbituric acid reactive substances formation.

Results The results of the study showed that the administration of 3 mg/kg indomethacin immediately after spinal cord trauma induces lipid peroxidation in a significant degree ($p < 0.018$) in comparison to the control group.

Conclusion This suggests that indomethacin may be harmful in spinal cord trauma.

Key words Free radicals, indomethacin, spinal cord trauma.

Introduction

Spinal traumas were initially managed by Hippocrates with a simultaneous traction applied to the shoulders and hips. This method, with some little modifications, had been used till early 1900's. Beginning of this century was to introduce new methods in management of spinal cord injuries by the great support of radiological discoveries (1). In this half of the century the increasing rate of motor vehicle collisions and sport or work-accidents resulted spinal cord injury especially in young-age group, bringing up serious social and economical problems (2).

Many experimental and clinical studies performed in the recent years give attention to radical oxygen metabolites (ROM) accruing of playing role in etiopathogenesis of traumatic, ischemic, hemorrhagic, inflammatory and degenerative diseases of the systems, as well as the central nervous system (3-25).

Based on experimental studies, a secondary damage following the primary injury of direct trauma comes to be more representative of cell death. It is demonstrated that the secondary damage is due to multicentric biochemical reaction-chains provoking each other (8,10,15,26-32). These reports raise the hope to prevent the secondary damage in neural tissue evoked by

ROM, using pharmacological agents. Considering insufficiencies in the management of spinal cord trauma through so many years, the great importance of experimental studies is obvious.

In this study, holding in mind the underlying mechanism in secondary damage of neural tissue after ischemic and traumatic processes, we investigated and discussed the effects of indomethacin (IND), a member of nonsteroid anti-inflammatory drugs (NSAID), in experimental spinal cord trauma.

Different experimental trauma models are employed for the study of disorders in acute spinal cord trauma. Details of drop-weight method and compression with a constant weight for a definite time have been described in previous reports (6,30,33,34,35). However, a standard trauma may not be accomplished on the cord since the space of weight-contact is quite variable in these methods. To present a more standardized method, epidural balloon (6,35) or applying aneurysm clip (28,29,36,37) were proposed and it was demonstrated that clip using is the best in comparison (28,38).

Material and Method

In pharmacokinetic studies it is found that a 3 mg/kg intraperitoneal (i. p.) dose of IND reaches maximum serum concentration (13 µg/ml) in 10 minutes, dropping to 8 µg/ml in 30 minutes, 6 µg

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/ml in 60 minutes, 4 µg/ml in 90 minutes (9). In human beings, reports Bannwarth et al (39), after single dose of 50 mg. i.m., IND passes blood-brain barrier in 30 minutes and reaches a higher level than the serum concentration in BOS in 2 hours. The pharmacokinetic characteristics are also studied with high performance liquid chromatography (HPLC) (40).

In this experimental study, eighty females Albino-Wistar rats, weighing 160-200 g. were used. The animals were randomly divided in two main groups of forty (A= control group B= application group). In application group, 3mg/kg i. p. indomethacin (INDOCID®, Merck Sharp and Dohme, France) was given to the rats immediately on opening the clip. The control group didn't receive any injections of vehicle or something else.

The main groups were assigned to the subgroups of eight each considering the time to stop the biochemical reactions by the application of liquid nitrogen to the spinal cord after trauma in A1-B1 = 1. minute, A15-B15=15. minute, A30-B30=30. minute, A60-B60=60. minute, A90-B90=90. minute.

The rats were anesthetized by intraperitoneal administration of 50 mg/kg sodium thiopental (Pentotal Sodium®, Abbott, Turkey). The thoracic region was exposed by midline incision. Using operation microscope, the paravertebral muscles were dissected bilaterally and T5-T10 total laminectomy was performed. Care was taken not to cause spinal cord injury, if injury occurred, the

rat was omitted from the study. An extradural aneurysm clip (Yaşargil aneurysm clip, FE 740K, closing force =150 gms., Aesculap®, Germany) was applied as to capture the whole spinal cord transversally side to side, close to the middle of laminectomy site. Exactly one minute later, the clip was opened. The rats all became paraplegic. In application group (B), 3 mg./kg i. p. IND was given immediately on opening the clip. At planned times, biochemical reactions in the spinal cord and paravertebral tissues were stopped by application of liquid nitrogen. The spinal cord was dissected and placed in liquid nitrogen. It was covered with aluminum foil, numbered, taken into a falcon tube and immersed in liquid nitrogen tank.

To assess the lipid peroxidation levels, an indirect method, thiobarbituric acid (TBA) test was used (24,27,29,31,41). The frozen neural tissues were taken out and weighed, in a ratio of 10% put into 10% trichloro acetic acid (TCA) and mixed by ultrasonic vibration to obtain homogenate. This homogenate was centrifuged (4000 cycle /min) at +4°C for 15 minutes. 0.5 cc from the supernatant was mixed with 0.5 cc 67% TBA. The mixture was put into boiling water bath for 15 minutes. A pinkish color occurred. Thiobarbituric acid reactive (TBAR) substances absorption values were determined with spectrophotometer (Shimadzu®, UV-150-02), at 532 nm. The results were statistically appraised by ANOVA (Analysis of Variance) test.

Results

Table 1. Absorption values of thiobarbituric acid reactive substances

Groups	min 1	min 15	min 30	min 60	min 90
Control Group (A)	(A1) 0.061 0.069 0.070 0.077 0.080 0.085 0.088 0.137	(A15) 0.067 0.072 0.090 0.093 0.095 0.118 0.118 0.136	(A30) 0.074 0.077 0.077 0.078 0.091 0.093 0.097 0.115	(A60) 0.060 0.063 0.080 0.092 0.098 0.107 0.117 0.123	(A90) 0.066 0.069 0.078 0.083 0.085 0.128 0.131 0.140
Mean	0.0834	0.0986	0.0878	0.0925	0.0975
Application Group (B)	(B1) 0.065 0.085 0.087 0.097 0.100 0.103 0.107 0.192	(B15) 0.070 0.088 0.091 0.097 0.099 0.107 0.119 0.263	(B30) 0.070 0.071 0.080 0.089 0.091 0.093 0.118 0.124	(B60) 0.083 0.084 0.089 0.122 0.162 0.173 0.184 0.257	(B90) 0.070 0.084 0.093 0.096 0.097 0.107 0.107 0.122
Mean	0.1045	0.1168	0.0920	0.1443	0.0970

Table 2. Results of statistical test

Source of variation	Sum of squares	Degrees of Freedom	Mean-square	F	P
Main Effects	.016	5	.003	2.553	.035
Time	.009	4	.002	1.733	.153
Group	.007	1	.007	5.832	.018
2-Way Interactions	.007	4	.002	1.361	.256
Residual	.086	70	.001		
Total	.109	79	.001		

In Table 1, the absorption values obtained from groups A and B are shown. When the absorption values in groups A and B are compared statistically, the values in application group are significantly higher than those in control group (Table 2, $p=0.018$).

Also in Table 1, the mean absorption values are calculated. The highest mean absorption value (0.1443) presents in subgroup B60. The lowest absorption value (0.0834) presents in subgroup A1.

Discussion

The higher amounts of lipid content in neural tissue give the impression that the harmful effect of lipid peroxidation process caused by ROM should be stronger than in other tissues. Mainly by ROM, lipid peroxidation in cell membrane causes breaks in phospholipids and accumulation of arachidonic acid (AA). Following biochemical reactions generate AA metabolites. AA metabolites induce free oxygen radical formation, and also directly cause secondary damage [4,9,14,20-22,25-27,42-52].

In an effort to reduce secondary damage, NSAID are suggested, also indomethacin from NSAID, for known effects in AA metabolism and lipid peroxidation. Some known effects as cyclo-oxygenase enzyme inhibition, phospholipase A2 inhibition, directly OH scavenging and metal ions binding imply a possible benefit to prevent secondary damage (7,9,16,18,21,23,24,31,43,47-50,53-58).

On the other hand, IND induces oxygen radical formation in neutrofls (5,59,60) and carries the potential of own-oxidation to form any active radical (61) to be harmful. Because of this paradox, we thought it would be interesting to study with IND.

To achieve spinal trauma, we used aneurysm clip, reported to achieve more standardized trauma than the other techniques (28,38). We preferred drug administration after trauma. Hence, we get the chance of using drugs in human beings only after trauma and this may reliably reflect the clinical applications. When investigating the

relationship between lipid peroxidation level and time, we based on the previous studies (51,62). We preferred the TBA test which is widely used in assessing the amount of TBAR substances, to show the level of lipid per-oxidation, since technical difficulties in some other techniques (e. g. spin resonance spectroscopy) are reported (11,24,27,29,31,37,41,61).

The data (Table 1) reflects the higher levels of TBAR substances in application group are statistically significant ($p=0.018$) and show that IND increases the peroxidation of cell membrane phospholipids, if used as above. When the effects of IND via time are examined, TBAR substances pick up at minute 60 (means lipid peroxidation reaches the highest level in 60 minutes). However, the comparison between the mean absorption values due to time is statistically insignificant, only a slight pick at minute 15 is present. (ANOVA $F=1.733$ $P=0.153$)

Numerous investigations have been undertaken in an effort to show the benefits of IND. Since the extremely complicated mechanisms in secondary injury of spinal trauma are considered, it seems the known and unknown effects of IND process. It is demonstrated that some NSAID and IND induce the oxygen radical formation in human neutrofls via inhibition of diacylglycerol (DAG) lipase enzyme (5,59,60). Halliwell et. all. (61) proposed that, in attention to some NSAID (e. g. penicillamin reacts with OH and HOCl to form sulphur radicals) IND may form its own-radical by a similar mechanism. In this way, IND may provoke lipid peroxidation as a result of inducing oxygen radical formation in posttraumatic neutrofl aggregation, or reacting with OH and HOCl ions to form any other toxic radicals.

Conclusion

The literature exhibits a lot of reports on useful effects of IND and very few on harmful characteristics. Our study shows that IND increases the secondary damage after experimental acute spinal cord trauma by elevation in posttraumatic lipid peroxidation. These prove the harmful effects in controversy to be dominant.

It is necessary to plan more experimental studies since underlying mechanisms of posttraumatic injury are extremely complicated and to discuss the subject on coming investigations.

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