

# Effect of nonsteroidal antiinflammatory drugs in the prevention of postoperative adhesions

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*The role of NSAİ drugs in the prevention of postoperative adhesions was researched in rats after standard peritoneal injury. A total of 44 rats were divided into 4 groups, one of which received placebo and other three had high doses of ibuprofen, naproxen and tenoxicam, all administered intramuscularly. The mean adhesion scores were  $2.2\pm 0.5$  in the control group, and  $0.6\pm 0.3$ ,  $1.5\pm 0.3$ , and  $2.0\pm 0.3$  in the treatment groups, respectively. Ibuprofen appeared as the most effective drug in prevention of adhesions ( $p<0.05$ ). The relatively high rate of side effects at high doses precludes its clinical use as the primary means of treatment. However, ibuprofen can be used in certain cases as an adjunct to meticulous surgical technique and to other preventive measures. [Turk J Med Res 1993; 11(5): 217-220]*

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Postoperative abdominal adhesions are one of the common problems whose solution is being searched for years. Inflammation and reduction of fibrin accumulation, acceleration of fibrinolysis and suppression of collagen synthesis by fibroblast proliferation are the main effects of adhesion preventing methods (1-3). Prostaglandins and leukotriens play important role in the inflammatory reaction to tissue damages (3-5). These early mediators increase oedema by local blood flow, and exudation caused by vascular permeability (3,5). Up to this day, in neutralizing these effects which are the first steps of adhesion formation and preventing other stages of inflammation many materials have been used, and some NSAİ agents have also been tried (6,7). However, the number of studies introducing a comparative evaluation of the NSAİ agents being researched is very few (8). In this experimental study, the effects of three NSAİ drugs - namely ibuprofen, naproxen and tenoxicam - on prevention of abdominal adhesions has been investigated.

## MATERIALS AND METHODS

This study was done on 44 Swiss albino rats whose average weight was 215 g (190-240). The rats were

separated into 4 groups, one of which was the control group and the other three experiment groups. After ether anesthesia, standard surgical operations were done in sterile conditions on the rats to whom no food was given the night before. The powder on the gloves was cleaned by washing thoroughly with serum physiologic. Laparotomy of medium line section of 2 cm length was done on all the rats. Standard peritoneal damage was formed by rubbing a sterile toothbrush 5 times in the same direction on a 2 cm part of the terminal ileum which was 2 cm more proximal than the iliocecal resultant (9). The periton and the fascia were stitched with 4/0 crome catgut and the skin with 3/0 continuous silk stitches. In the first 6 hours the rats were not given anything orally.

The following dosages of the drugs were applied to the rats intramuscularly (IM), to the first group ibuprofen (35 mg/kg/day) (6); to the second group naproxen sodium (20 mg/kg/day) (10); and tenoxicam (25 mg/kg/day) (11) to the third. Since ibuprofen and naproxen sodium are not soluble in water, the 96% ethyl alcohol solutions of these materials were used (12,13). Serum physiologic solution of tenoxicam was used in its ready-made injectable form. The first doses of placebo and the test drugs were first given 2 hours before, and the second doses 6 hours after the operation. Later tenoxicam was given once a day, summing up to a total of 7 doses, and the other two drugs were given twice a day totalling to 12 doses. To ensure uniformity among all groups, the rats in the control and tenoxicam groups were injected intramuscularly 0.5 ml

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of 96% ethyl alcohol for a total of 12 times. The rats were killed on the 7<sup>th</sup> day by an overdose of ether inhalation and were taken to relaparatomy. One of the writers who did not know the grouping, checked for adhesions in the reference region and graded the adhesions in the style Mazuji et al (14) had proposed. After the average adhesion scores of each group was obtained the differences between the groups were investigated using Wilcoxon Rank Sum test.

## RESULTS

Two rats, one in the control group and the other in the ibuprofen group were left out of the experiment since they had died during the first two days. No adhesions of 4<sup>th</sup> degree was seen on the subjects of this study. Adhesions were seen on 4(40%) of the rats in the ibuprofen group, 9(82%) of the rats in the naproxen group and 10(91%) of the rats in the tenoxicam group. All the subjects of the control group had adhesions. The adhesions in the ibuprofen and naproxen groups were light whereas the adhesions in the tenoxicam and control groups were severe. The average adhesion score in the control group was  $2.2 \pm 0.5$ , whereas in the ibuprofen group the score was  $0.6 \pm 0.3$ , in the naproxen group  $1.3 \pm 0.3$  and in the tenoxicam group  $2.0 \pm 0.3$  (Table 1). Ibuprofen was found to be more effective than placebo, naproxen sodium and tenoxicam in preventing adhesions ( $p < 0.05$ ). Among the other groups a meaningful difference could not be found ( $p > 0.05$ ). Almost all of the rats had edema, inflammation and sensitivity on their hips which was caused by injections and ethy alcohol irritation.

## DISCUSSION

It is known that adhesions following standard intestine damage mature following the stages of inflammation, exudation, fibroplasi and organization (4). On observation of microscopoc developments in the damaged region which follow the periton abrasion it is seen that first a fibrin network forms, then this network is surrounded by Leukocytes and monocytes; later maturing and proliferating fibroblasts begin collagen synthesis and finally capillary veining increases (3). Lawler (15), has shown that thrombocytes, which synthesize factors

accelerating fibroblast maturation, play an important role in the formation of adhesions. Whereas Shimonuki (16) has pointed out the importance of arachidonic acid metabolism in the macrophages, in the healing of peritoneal wounds.

In the formation of a cellular reaction to tissue damage prostaglandins and other arachidonic acidic metabolys are very important (1,4,17). These factors which increase local blood flow, vascular permeability and exudation have an important role in the early stages of inflammations (4,17). On the other hand NSAİ drugs inhibit cyclooxygenase thus inhibiting prostaglandine synthesis (4,18,19). Thrombocyte aggregation and function is also inhibited by NSAİ drugs (3,4,6). Some of the drugs belonging to this group also suppress lipooxygenase (18,19). This inhibition slows down the synthesis of leukotriens which are the products of lipooxygenase activity and are the cause of the beginning or the change of direction of many biochemical events taking place in the muscular, venal, epithelial cells and leukocytes (17,19,20).

In the prevention of adhesions on rats and rabbits, on whom standard coroz defect has been formed ibuprofen has an effect equal to that of indomethacin (3) and stronger than that of other NSAİ drugs (1,4,7,8,9,21). No study dealing naproxen and tenoxicam has been in the literature. In our study ibuprofen has both decreased the number of and the severity of the adhesions. It must be noted that naproxen has a weak effect in both aspects and that the results obtained with tenoxicam are the same as the results obtained in the control group. High dosages of all three drugs have been used and the differences in their effects can probably be explained by the differences in their effect mechanisms. It is known that tenoxicam like other oxicams has a weak effect in prostaglandine inhibition (11). The effect on the lipooxygenase system of these three drugs which are known to be effective on cyclooxygenase is not known exactly. Prostaglandine E<sub>1</sub> (PGE<sub>1</sub>) and PGE<sub>2</sub> which are the products of cyclooxygenase activity inhibit the synthesis of leukotrien which is a lipooxygenase metabolite (22). Elliott et al (23), have demonstrated that aspirin and indometasine while inhibiting cyclooxygenase leukotrien B<sub>4</sub> synthesis indirectly. The

Table 1. Mean adhesion scores in control and treatment groups (21)

Treatment groups	Total no. of rats	Adhesion score					Mean adhesion score $\pm$ SD*	
		0	+1	+2	+3	+4		
Control	10	0	2	4	4	0	$2.2 \pm 0.5$	—
Ibuprofen	10	6	2	2	0	0	$0.6 \pm 0.3$	<0.05
Naproxen	11	2	<b>rjof</b>	7	0	0	$1.5 \pm 0.3$	>0.05
Tenoxicam	11	1	2	4	4	0	$2.0 \pm 0.3$	>0.05

\* Standard deviation of the mean

\*\* Wilcoxon Rank Sum Test

differing effects of the NSAİ drugs used in this study on preventing adhesions may be related to the differences of their inhibitions on the lipooxygenase enzyme system. Since the mechanisms of the effects of these drugs have not been understood completely, it is not possible to put forward any further explanation.

The adhesion reductive effect of ibuprofen depends on the first application time and dosage. When the first dose is applied in the preoperative stage considerable decrease in microscopic damage diagnoses is noted (1). When first applied in the postoperative stage its effect is reduced to the level of placebo (6). As the dosage of applied ibuprofen is increased its effect increases noticeably (4,6). In our study the first dose of the drugs has been applied 2 hours before, the second 6 hours after the operation and the dosages have been kept quite high.

In our opinion, ibuprofen and other NSAİ drugs should not be considered as elements of a fundamental therapy in the prevention of adhesions, because despite the high application dosages and the clear difference in the mesotelial cellular response it has not been possible to prevent adhesions completely with these therapy method. Furthermore, applying these drugs in high dosages causes some side effects. According to our observations in this study, ibuprofen is more successful in the prevention of adhesions when compared to other NSAİ drugs. Therefore ibuprofen can be used in certain cases as an adjunct to meticulous surgical technique and to other preventive measures.

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Postoperatif yapışıklıkların önlenmesinde nonsteroidal antiinflamatuar ilaçların rolü

*Postoperatif yapışıklıkların önlenmesinde nonsteroidal antiinflamatuar (NSAİ) ilaçların rolü bu deneysel çalışmada araştırıldı. Standart periton hasan yaratılan 44 sıçan 4 gruba ayrıldı. Kontrol grubundakilere serum fizyolojik, diğerlerine ise ibuprofen, naproksen ve tenoksikam intramüsküler verildi. 7. günde ortalama yapışıklık skorları kontrol grubunda  $2.2 \pm 0.5$ , diğer gruplarda ise sırasıyla  $0.6 \pm 0.3$ ,  $1.5 \pm 0.3$  ve  $2.0 \pm 0.3$  idi. Yapışıklıkların önlenmesi yönünden ibuprofen, plasebo ve diğer iki NSAİ ilaçtan daha etkili bulundu ( $p < 0.05$ ). Yapışıklıkların önlenmesinde ibuprofenin, titiz cerrahi tekniğe yardımcı bir ajan olarak kullanılabilceği düşünüldü. [Turk J Med Res 1993; 11(5): 217-220]*

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