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Haemostatic Effects of Ketorolac with and without Concomitant Heparin in Normal Volunteers

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Key words

Ketorolac – Heparin – Kaolin cephalin clotting time

Summary

Ketorolac is a potent cyclo-oxygenase inhibitor used for the treatment of postoperative pain. It is known to have anti-platelet properties. The aim of this study was to determine the effect of ketorolac on haemostasis both alone and in combination with low dose heparin in 12 healthy male volunteers. Each volunteer received the following drug combinations in a double blind, placebo controlled, cross over manner: ketorolac placebo/heparin placebo, ketorolac active/heparin placebo, ketorolac active/heparin active and ketorolac placebo/heparin active. Ketorolac significantly prolonged bleeding time, inhibited platelet aggregation to arachidonic acid and collagen and platelet thromboxane production. Heparin had no effect on bleeding time or platelet function, but significantly prolonged the kaolin cephalin clotting time and increased anti-Xa levels. Ketorolac had no effect on the kaolin cephalin clotting time or anti-Xa levels and no interaction was found between ketorolac and heparin in any of the investigations. The prolongation of bleeding time seen with ketorolac is unlikely, to be of any major clinical significance as almost all subjects remained within the normal range; however, it should be used with caution in subjects with haemostatic problems.

Introduction

Ketorolac tromethamine (ketorolac) is a cyclo-oxygenase inhibitor which has potent analgesic properties. It can be given orally or parenterally and has been used successfully in the treatment of post-operative pain (1, 2, 3, 4). It has been used on its own – as an alternative to opiates (1, 2) and in conjunction with opiates (3). In the latter situation an opiate sparing effect occurs, so minimising the side effects of opiate therapy.

As ketorolac inhibits cyclo-oxygenase activity it will block TxA_2 production and inhibit platelet aggregation (5). This may interfere with the haemostatic response.

Low dose sub-cutaneous heparin is widely used as prophylaxis against deep venous thrombosis (DVT) following surgery. It acts by stimulating the anti-coagulant properties of anti-thrombin III. This inhibits the development of thrombosis, however, it can also interfere with the haemostatic response, although haemorrhagic problems appear to occur infrequently and are seldom of clinical importance with low doses of heparin (5,000 i.u. bid) given subcutaneously for post-operative DVT prophylaxis (6).

Ketorolac and heparin can both interfere with the haemostatic response, and may be used simultaneously post-operatively as analgesia and DVT prophylaxis respectively. The aim of this study was therefore to assess the effect of ketorolac on haemostasis both alone and in combination with low dose heparin in healthy volunteers.

Subjects, Materials, and Methods

Twelve healthy male volunteers were studied. Baseline haemostatic data and demographic information were collected prior to the commencement of any treatment. The subjects were then allocated to receive each of the following drug/placebo combinations in a double blind randomised cross-over manner. The drug/placebo combinations were: ketorolac placebo/heparin placebo, ketorolac active/heparin placebo, ketorolac placebo/heparin active and ketorolac active/heparin active. A latin square design was used with the same latin square used for 3 groups of 4 volunteers so that the effect of the treatment sequences could be studied. By the end of the study, therefore each volunteer had received each combination once. The interval between each treatment was 1 week. During the course of the study no subject took any other drugs.

The drugs/placebos were administered as follows. On the evening prior to the study each volunteer took a capsule of 10 mg ketorolac or placebo and repeated this the following morning on rising. At 10 a.m. and 2 p.m. on the day of the study each volunteer then received an intramuscular injection of 10 mg ketorolac or placebo into the deltoid muscle and 5,000 i.u. of heparin or placebo given subcutaneously into the abdominal wall. Matching placebos for both were used so that all four combinations appeared identical.

On each study day venous blood was withdrawn without stasis using a 21 gauge butterfly canula at 13.45 hours and at 16.00 hours to study the effects at trough and near peak concentrations of ketorolac respectively. The latter time was in keeping with the expected time of peak plasma concentrations of the drug as determined by previous pharmacokinetic studies. A bleeding time was also performed on each study day at 16.00 and blood from the bleeding time site collected for measurement of TxB_2 production.

Skin bleeding times were performed in duplicate on the forearm by the method of Ivy et al. (7) using a Simplate II bleeding time device. The bleeding time was recorded for each wound and the mean calculated.

Blood from bleeding time wounds was collected at 1 minute intervals using capillary tubes (approximately 50 µl of blood/minute). These were sealed and kept at 37° C for 1 hour then centrifuged at 3,000 rpm for 15 minutes at 4° C to stop the reaction. The resultant serum was diluted 1:400 using assay buffer (0.1 M phosphate buffer pH 7.0 with 0.1% bovine albumen) and TxB_2 measured by radioimmunoassay as previously described (8). The lower limit of the assay was 20 pg/ml, intra-assay variation was 4% and inter-assay variation was 10%.

Whole venous blood was anti-coagulated with 3.2% trisodium citrate 1 part anticoagulant to 9 parts blood. Platelet aggregation was assessed using the Clay-Adams Ultra-Flo 100 whole blood platelet counter as previously described (9). Platelet count was determined immediately prior to the addition of the aggregating agent (baseline) and 5 minutes following addition of the aggregating agent. At all times 2 platelet counts were taken and the total fall in platelet count from time 0 to 5 minutes calculated. Two aggregating agents were used, collagen 1 µg/ml (Hormon-Chemie) and arachidonic acid 0.5 mM (Sigma). In addition a similar experiment with only the aggregating agents vehicle was performed to study any effect on spontaneous aggregation.

TxB_2 generation from whole blood was measured on venous blood at trough and near peak ketorolac plasma concentrations. A 1 ml aliquot was placed in a glass test tube with no anticoagulant and allowed to clot spontaneously for 60 minutes at 37° C. The reaction was halted and serum

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Table 1 Skin bleeding time test results for all subjects by treatment combination

	Heparin placebo			Heparin active		
	Mean ± SD	Min	Max	Mean ± SD	Min	Max
Ketorolac placebo	311.8 ± 95.4	210.0	512.5	338 ± 92.5	207.5	477.5
Ketorolac active	406 ± 158.8	228.0	730.0	457 ± 292.5	191.0	1290.0

n = 12 for all measurements.

obtained by centrifugation at 3,000 rpm for 15 minutes at 4° C. The serum obtained was assayed for TxB_2 by radioimmunoassay as previously described (10).

Heparin activity was assessed by KCCT and anti-Xa activity which were measured in plasma obtained from venous blood anti-coagulated with 3.2% trisodium citrate. The KCCT was measured by a clotting assay using the Organon Teknika X_2 Coag-a-mate and anti-Xa activity was assessed using a chromogenic substrate assay (Kabi-Vitrum).

Statistical Analysis

The skin bleeding times were analysed within a factorial model framework with the intention of looking for the separate effects of ketorolac and heparin, together with any interaction effects between the two. In addition the skin bleeding time on ketorolac placebo was correlated with the skin bleeding time on active ketorolac. To form paired data amenable to analysis the combination ketorolac/heparin was compared with placebo/heparin whilst ketorolac/placebo was compared to placebo/placebo to form 24 observations with each subject providing 2 observations. The Spearman rank test was used to assess correlation.

The results of thromboxane B_2 (TxB_2) measurement in the blood from the bleeding time were analysed by taking the median value of all observations for each patient. These values were compared for the different treatment combinations, and were also investigated in respect of correlations to the mean bleeding time. The number of TxB_2 samples obtained from the bleeding time wound was investigated for any treatment effect using a factorial model, as a measure of blood volume, since approximately 50 µl was taken each time in each sample.

For the platelet function test the change from baseline to five minutes was calculated in an analysis of variance (ANOVA) model. This was carried out separately for the tests at the times corresponding to near peak and trough plasma concentrations of ketorolac.

The median serum concentration of TxB_2 and the range of concentrations were tabulated for comparison, but no statistical analysis was found to be necessary to separate treatment effects.

The KCCT values were examined for results at both near peak and trough plasma concentrations of ketorolac using ANOVA. The results for both placebo and active heparin treatment periods were then correlated with the bleeding time results, to look for the effect of KCCT on bleeding time.

The results for anti factor Xa were tabulated showing the median results and range for each treatment combination. Wilcoxon signed rank tests were performed to examine whether active heparin produced a different anti Xa result than the placebo heparin. The anti Xa results at near peak and trough plasma concentrations of ketorolac were again analysed separately. To form paired data amenable to analysis, the combination ketorolac/heparin was compared with the combination ketorolac/placebo to form 12 observations, whilst placebo/heparin was compared with placebo/placebo to form an additional 12 observations. Hence each test was based on 24 differences active heparin minus placebo, with each of the subjects providing 2 observations.

Results

Subjects

The mean age of the subjects under study was 24.3 ± 3.0 (SD) years (range 20–30 years), the mean height was 178.4 ± 7.2 (SD) cm (range 165–190.5 cm) and the mean weight was 75.9 ± 11.7 kg (range 63–102 kg).

Skin Bleeding Times

There was a significant prolongation of bleeding time with active ketorolac but heparin either alone or combined with active ketorolac had no significant effect on bleeding time (Table 1). The skin bleeding time was found to increase by a mean of 106 seconds when active ketorolac results, combined over both heparin treatments were compared to placebo ketorolac combined over both heparin treatments. This represented a 32.5% increase which was statistically significant ($p = 0.021$) in the ANOVA model; the 95% confidence interval was calculated as 18 seconds to 195 seconds (5.4% to 60.1%). The result for active heparin compared to placebo heparin was not significant ($p = 0.378$). The bleeding time on active ketorolac correlated with the bleeding time on placebo ketorolac ($r = 0.498$; $p = 0.013$).

The mean results shown on Table 1 give no evidence for any interaction between ketorolac and heparin ($p = 0.786$), but display a greatly increased standard deviation (292.5) in the active/active combination. This is mainly due to one subject who recorded a bleeding time of 1,290 seconds following this combination, although there is a general increase in the spread of data.

In view of this subject's exceptionally long bleeding time on the combination of active ketorolac and active heparin, he was recalled and bleeding time repeated after treatment with the same combination. On this occasion his bleeding time was 480 seconds. As the initial result was not reproducible and was out of keeping with the response of other subjects the initial result may have been spurious.

Thromboxane B_2 from the Bleeding Time Wound

There was a clear differentiation between the TxB_2 values recorded for active ketorolac and those recorded for placebo ketorolac, with median values being 8 ng/ml and approximately 400 ng/ml respectively (Table 2). All the recordings for ketorolac active were considerably less than the median for the placebo/placebo group and they were all less than the lowest value of 216 ng/ml in the placebo/placebo group. There was no suggestion of either a heparin effect on TxB_2 or of any interaction of heparin with active ketorolac.

The median TxB_2 from the bleeding time wound was correlated with the mean skin bleeding time in two separate correlations, one for active ketorolac and one for placebo ketorolac. A Pearson correlation coefficient (r) of −0.263 ($p = 0.214$, $n = 24$) was obtained for placebo ketorolac and was not statistically significant. The corresponding result for active ketorolac was −0.442 which was significant ($p = 0.031$), indicating a negative relationship between TxB_2 and bleeding time.

The analysis of the number of TxB_2 samples obtained, to give a measure of the volume of blood loss, showed a significant ketorolac effect on the number of samples ($p = 0.004$). Ketorolac increased the number of samples by a mean value of 1.92 (confidence interval 0.67–3.17) representing a 52.3% increase. Heparin did not show a significant interaction with ketorolac ($p = 0.686$).

Arachidonic Acid-Induced Platelet Aggregation

At trough concentrations of ketorolac, the presence of active ketorolac reduced platelet aggregation by 80.7×10^9 platelets/litre (44.6%) (95% confidence limits = 61.6×10^9 platelets/litre to 99.4×10^9 platelets/litre) while at near peak levels, the reduction was 69.5×10^9 platelets/litre (36.8%) (95% confidence limits = 46.5×10^9 platelets/litre to 92.5×10^9 platelets/litre), when compared to the platelet aggregation when placebo ketorolac was present. The extent of platelet aggregation following ketorolac treatment was significantly different from that

Table 2 TxB_2 production from bleeding time wounds and whole blood clotting

Near concentration	TxB_2 production from bleeding time wounds (ng/ml)		TxB_2 production from whole blood clotting (ng/ml) At ketorolac trough concentration		At ketorolac peak	
	Median	Range	Median	Range	Median	Range
Ketorolac/heparin	8	4–8	7.6	4–28	4.0	4–56
Ketorolac/placebo	8	4–9.6	11.0	4–70	9.0	4–220
Placebo/heparin 216–400	352		224–400	400	4–400	400
Placebo/placebo	395	216–400	400	216–400	400	76–400

Table 3 Effect of ketorolac and heparin on platelet aggregation. Mean (± SD) fall in platelet count from baseline to 5 minutes

		Arachidonic acid (0.5 mM) induced aggregation		Collagen (1 μg/ml) induced aggregation		Spontaneous aggregation	
		Heparin placebo	Heparin active	Heparin placebo	Heparin active	Heparin placebo	Heparin active
Peak ketorolac sampling time	Ketorolac placebo	84.8 ± 38.4	192.5 ± 44.5	151.4 ± 45.2	161.0 ± 51.2	23.6 ± 23.7	30.6 ± 23.6
	Ketorolac active	110 ± 40.0[3]	127 ± 38.3[3]	62.8 ± 43.9[2]	71.3 ± 38.4[2]	13.3 ± 16.1[1]	16.0 ± 17.2[1]
Trough ketorolac sampling time	Ketorolac placebo	178.4 ± 46.2	180 ± 33.8	151.7 ± 43.9	135.8 ± 52.6	30.5 ± 28.3	18.5 ± 19.5
	Ketorolac active	92.5 ± 31.9[3]	104.5 ± 44.3[3]	44.1 ± 23.0[3]	61.8 ± 31.3[3]	18.3 ± 15.6	24.0 ± 23.1

n = 12 for all measurements.
Values shown are $\times 10^9$ platelets/litre.
[1] $p < 0.05$
[2] $p < 0.001$
[3] $p < 0.0001$
} active ketorolac compared to placebo.

produced following placebo ($p < 0.0001$ at both peak and trough levels). These data are shown in Table 3.

Heparin had no effect at either testing time. There was no evidence of an interaction effect between ketorolac and heparin at near peak or trough concentrations of ketorolac.

Collagen-Induced Platelet Aggregation

Similar results were obtained for collagen induced platelet (Table 3) aggregation as for arachidonic acid induced aggregation. Active ketorolac inhibited aggregation compared to placebo ketorolac. The result was highly significant for both near peak ($p < 0.001$) and trough ($p < 0.0001$) concentrations of ketorolac. At peak concentrations the change was 89.2×10^9 platelets/litre which was a 57% reduction in platelet aggregation when compared to placebo (95% confidence limits = 62.6×10^9 platelets/litre to 115.8×10^9 platelets/litre), and at trough concentrations the reduction was 90.4×10^9 platelets/litre (61.8%), with confidence limits of 72.5×10^9 platelets/litre to 108.4×10^9 platelets/litre.

Spontaneous Platelet Aggregation

The only statistically significant result found was at the peak concentrations timing, when the presence of ketorolac inhibited platelet aggregation by 45.8%, significantly different from the result observed with placebo ($p = 0.033$). The inhibition over 5 minutes was 12.4×10^9 platelets/litre (95% confidence interval: 1.0×10^9 platelets/litre to 23.8×10^9 platelets/litre). There was no significant inhibition of spontaneous aggregation due to the presence of heparin, and there was no evidence of an interaction between the two drugs.

Thromboxane B_2 Generation from Whole Blood

The results of the radioimmunoassay of TxB_2 produced from whole blood clotting reveal a clear distinction between active and placebo ketorolac at both testing times. Table 2 shows the median and range of values. In the presence of ketorolac, serum TxB_2 concentration was greatly reduced. Heparin had no effect on TxB_2 generation and there was no evidence of any heparin/ketorolac interaction. There was no significant difference between the two test times (near peak and trough).

Kaolin Cephalin Clotting Time (KCCT)

There was no evidence of any effect of ketorolac on KCCT at either testing time ($p = 0.633$ at trough and $p = 0.978$ at near peak times).

A highly significant ($p < 0.0001$) heparin effect was obtained at the near peak testing time, such that the heparin increased KCCT by 6.7 seconds (95% confidence interval = 3.6 to 9.8 seconds) which represented a rise of 21% from the placebo heparin level of 31.9 seconds. There was no significant heparin effect at the trough testing time ($p = 0.137$). There was no evidence of an interaction effect between ketorolac and heparin at either time.

The results of KCCT tests are shown in Fig. 1. KCCT values were examined for any correlation with the bleeding time. The correlations were examined separately for active and for placebo heparin, and for the two testing times. No significant correlation was found for either active or placebo at either time.

Anti-Xa Activity

Median values and ranges for the anti-Xa results are shown for each treatment combination in Table 4. The statistical analysis of

the data found that as expected anti-Xa was significantly higher for active heparin when compared with placebo, both a trough ($p < 0.001$) and at near peak ($p < 0.01$) times. Ketorolac had no effect on anti-Xa.

Adverse Effects

Minor bruising was noted at several injection sites but there was no difference between any of the treatment combinations. No other adverse effects occurred.

Discussion

This study has shown that ketorolac as expected will significantly prolong bleeding time. In general this is a modest prolongation similar to that seen with aspirin. It is unlikely to be of any major clinical significance (10), as almost all the subjects' bleeding times stayed within the normal range following ketorolac (<10 minutes). However, there was a wider distribution of the bleeding time values after ketorolac. This suggests that normal subjects do not respond to ketorolac as a single population with some individuals showing a more marked prolongation of bleeding time. Heparin had no significant effect on bleeding time and there was no evidence of any interaction of heparin and ketorolac. One individual had a markedly prolonged bleeding time on heparin and ketorolac (>20 minutes) and this cannot readily be explained, as it was not reproducible when the same individual was studied again on the same treatment combination. The Ivy technique with the simplate device is an extremely reproducible technique and therefore is unlikely to account for such a discrepancy (11, 12). This raises the possibility that not only does ketorolac cause a heterogeneous response with regard to bleeding time prolongation in the population but also that the individuals response to ketorolac may be heterogeneous with the prolongation in bleeding time following ketorolac not being predictable on repeated testing of the same individual. Similar results on bleeding time are seen with aspirin in volunteers (11) both in terms of the mean and range of prolongation of the bleeding time. In addition the volume of blood lost from the bleeding time site was increased with ketorolac treatment. There was a positive correlation between bleeding time on ketorolac and bleeding time on placebo with a mean prolongation of bleeding time of around 33%. This suggests that some relationship between the response to ketorolac and the placebo bleeding time may exist.

While a drug with anti-platelet effects such as ketorolac is unlikely to cause significant bleeding problems in normal individuals even in the peri-operative situations, it is possible that the use of such an agent in patients with haemostatic problems such as thrombocytopaenia, haemophilia or von Willebrands Disease could result in haemorrhagic complications. In the clinical situation studies with ketorolac (1, 2, 3, 4) and non-steroidal antiflammatory agents (13) have not reported haemostatic problems. However, a study where aspirin and subcutaneous heparin were used in combination reported a high incidence of haemorrhagic complications in patients following surgery for hip fractures (14). The numbers reported in this study were small and larger well designed studies employing a combination of aspirin and subcutaneous heparin have not documented any increase in haemorrhagic complications (15, 16, 17).

It is likely that ketorolac exerts its influence on bleeding time by inhibiting thromboxane production and platelet aggregation, and the bleeding time following ketorolac administration correlated inversely with TxA_2 production. Heparin, because of its inhibitory effects on thrombin production may inhibit thrombin induced platelet activation. However, no effect was noted on TxB_2 production from whole blood allowed to clot spontaneously a situation where thrombin would be involved in the platelet activation. Heparin had no effect on platelet aggregation and no interaction with ketorolac was noted. As expected heparin significantly increased the anti-Xa activity when compared to placebo confirming that clinically significant anti-Xa levels were obtained. Heparin had no effect on bleeding time but significantly prolonged the KCCT at near peak concentrations. This increase in KCCT although statistically significant was not sufficient to cause the KCCT to increase beyond the upper limit of normal values. Again no interaction was found between ketorolac and heparin.

In conclusion this study has shown that ketorolac will prolong bleeding time by inhibiting thromboxane production and platelet aggregation. This prolongation of bleeding time is unlikely to be of any major clinical significance in normal individuals, but ketorolac should be avoided in patients with haemostatic problems. No interaction was found between heparin and ketorolac. However, as with any agent affecting haemostatic function, idiosyncratic responses may occur and due caution should be exercised in the concomitant clinical administration of these two drugs.

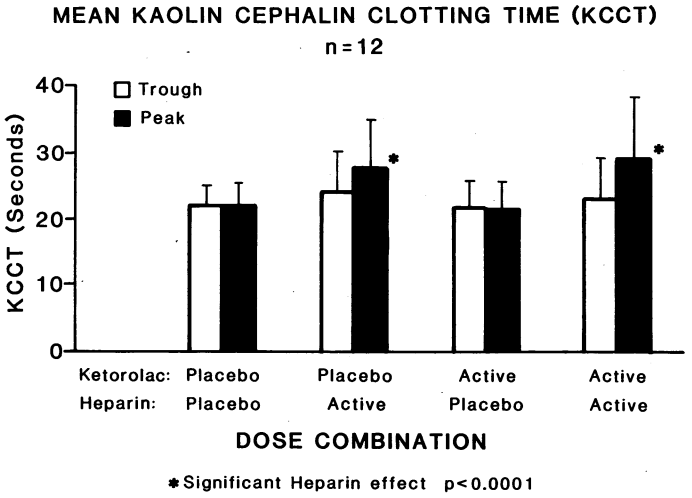

Fig. 1 Mean kaolin cephalin clotting times (KCCT) with one standard deviation shown for each of the four treatment combinations at near peak and trough concentrations

Table 4 Anti Xa results (U/ml)

Treatment combination	Test time 13.45 (trough)		16.00 (peak)	
	Median	Range	Median	Range
Ketorolac/heparin	0.0275*	0.0–0.12	0.065*	0.0–0.145
Ketorolac/placebo	0.0	0.0–0.1	0.0	0.0–0.03
Placebo/heparin	0.0225*	0.0–0.18	0.08*	0.025–0.185
Placebo/placebo	0.0	0.0–0.25	0.0	0.0–0.35

n = 12 for all measurements.
* $p < 0.01$: active heparin compared to placebo.

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