Comparing the effects of salts of diclofenac and almioprofen with aspirin on serum electrolytes, creatinine and urea levels in rabbits

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Abstract: The effects of diclofenac sodium, diclofenac potassium, alminoprofen and aspirin on serum electrolytes (serum Na^+ and K^+), urea and creatinine were compared in rabbits in acute and chronic phases of treatment. The data suggested that all the four drugs markedly increased the serum electrolytes, urea and creatinine levels in both post-treatment phases. In conclusion, present study does not present any advantage of diclofenac sodium over diclofenac potassium at electrolyte levels on short and long term treatment. Nevertheless, current data support the evidence of renal function impairment by all the four drug therapies used in the present study, which is generally caused by NSAIDS.

Keywords: NSAIDs, renal function, serum electrolytes.

INTRODUCTION

Inflammatory diseases including rheumatoid arthritis and osteoarthritis are initially treated with non-steroidal anti-inflammatory drugs (NSAIDS) (Patrono and Rocca, 2009). Previously, steroids were prescribed to manage the chronic inflammatory diseases, however, due to their severe adverse effects, NSAIDS has become the first choice to treat these diseases. Prolonged use of NSAIDS can also cause severe untoward effects, such as gastritis (Garcia Rodriguez and Barreales Tolosa, 2007), nephritis (Besen *et al*., 2009), cardiovascular and hematological disorders (Krotz and Struthmann, 2010). The sodium (Na^+) salt of diclofenac has been assumed to raise the serum electrolytes such as Na^+ which may affect hypertensive patients. Perhaps on this assumption, the potassium (K^+) salt of diclofenac is considered safer in the patients to avoid the rise in Na^+ levels. The effect of these different salts of diclofenac and other NSAIDS on electrolyte levels is not comprehensively reported. Thus, this study was designed to compare the effects of Na^+ and K^+ salts of diclofenac, in addition to alminoprofen, with acetyl salicylic acid on serum Na^+, K^+, urea and creatinine levels in rabbits.

Methodology

Drugs

Diclofenac Na^+, diclofenac K^+ (Novartis, Pakistan), alminoprofen (Highnoon Laboratories, Pakistan) and aspirin (Atco Laboratories, Pakistan) were kindly supplied.

Animals

Healthy albino rabbits (*Caprolagus hispidus*) of either sex, weighing 1.5 kg were included in the study. These rabbits were acclimatized for one week before commencement of experimental protocol. The rabbits were given fodder twice daily, while water was available *ad libitum*. Throughout the study, environmental conditions remained constant. Rabbits were divided into five groups, each of six animals. Same group of animals were used for acute and chronic phases of the study. In both studies, rabbits of each group were orally administered diclofenac Na^+, diclofenac K^+, alminoprofen, acetyl salicylic acid in a doses of 2.5mg, 2.5mg, 10 mg, 100mg/kg bw/day respectively. The control animals received vehicle.

Collection of blood

The blood samples were collected from ear marginal vein of rabbits and centrifuged to get serum. In acute phase of the study, animals were administered the drug only once and blood samples were drawn at 1, 2, 4, 6, 8 and 10 hours post-administration. However, before administration of any drug, the collected blood samples were considered as 0 hours. Similarly, in chronic phase, the drugs were administered once daily for 30 days and blood samples were collected on the subsequent 5, 10, 15, 20, 25 and 30 post-treatment days.

Analytical method

Estimation of serum Na^+ and serum K^+ levels were determined by colorimetric determination magnesium-uranyl acetate method and colorimetric turbidimetric test (Quimica Clinica Aplicada, Spain) respectively. Urea estimation was carried out by urea enzymatic spectrophotometric method (Bio Systems, Spain), whereas serum creatinine was determined by creatinine kinetic method (Biocon, Germany).

STATISTICAL ANALYSIS

The data obtained from both acute and chronic studies were subjected to Student's t-test, analysis of variance and Duncan's multiple range test where appropriate.

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RESULTS

Table 1 shows serum Na^+ levels of rabbits, which were administered all the drugs under investigation, in addition to vehicle. Zero hour readings were considered as 100%, whilst percentage serum Na^+ concentrations have been calculated at different time intervals. All the drug-treatments showed a significant increase ($P<0.01$) in Na^+ concentration at all hourly time-intervals, however the control (vehicle) group did not exhibit any change in the parameter. Table 2 displays the effects of drugs on day 5, 10, 15, 20, 25 and 30 on serum Na^+ levels. Similar to table 1, all the drugs exhibited a significant ($P<0.001$) rise in serum electrolyte levels, whilst vehicle did not show any change in the concentration of Na^+.

Table 3 exhibits a significant ($P<0.01$) increase in serum K^+ concentration with all the drug treatments except control. In table 4, similar pattern of profound ($P<0.01$) increase in serum K^+ levels was observed, while the control group of animals exhibited no significant change. Similarly, serum urea levels in acute (table 5) and chronic

Table 1: The serum sodium levels (mmol/l) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg), aspirin (100mg/kg) or vehicle. Serum levels were measured before (zero hours) and after administration of drugs on given hours.

Hours	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	113.64±1.59 (100%)	162.53±0.81 (100%)	195.37±4.68 (100%)	200.53±9.32 (100%)	148.92±1.87 (100%)
1	165.18±2.5** (145)	157.85±2.8 (97)	208.66±8.2** (107)	211.36±7.2** (105)	148.2±2.3 (99)
2	167.3±2.2** (147)	149.95±4.5 (92)	213.21±7.8** (109)	218.23±6.5** (109)	147.97±2.5 (99)
4	171.55±1.6** (151)	185.03±4.9** (114)	222.83±6.4** (114)	224.54±5.5** (112)	147.85±2.3 (99)
6	173.85±1.6** (153)	216.21±23.9** (133)	226.91±6.9** (116)	228.83±7.0** (114)	148.17±1.8 (99)
8	176.78±1.8** (155)	236.5±9.2** (146)	233.8±8.6** (120)	235.7.9±6.9** (118)	147.17±1.4 (99)
10	179.23±2.3** (158)	247.34±3.1** (152)	240.26±6.6** (123)	242.16±7.7** (121)	147.95±1.2 (99)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100% , **P<0.01

Table 2: The serum sodium levels (mmol/l) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg), aspirin (100mg/kg) or vehicle. Serum levels were measured before (zero hours) and after two hours of administration of drugs on given days.

Days	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	113.64±1.59 (100%)	162.53±0.81 (100%)	195.37±4.68 (100%)	200.53±9.32 (100%)	148.92±1.87 (100%)
5	133.34±1.3** (117)	158.6±2.9 (97)	227.46±10.1** (116)	240.75±10.0** (120)	152.17±1.7 (102)
10	163.78±2.2 (144)	149.95±4.5 (92)	213.21±7.8** (109)	264.13±14.1** (132)	147.97±2.5 (99)
15	167.6±2.2** (148)	170.11±13.1** (105)	241.5±3.1** (124)	233.96±4.8** (117)	151.15±1.7 (102)
20	171.53±2.6** (151)	219.02±25.2** (135)	219.45±8.4** (112)	214.66±8.6** (107)	151.02±1.4 (101)
25	177.76±3.5** (156)	257.94±7.9** (159)	210.43±7.5** (108)	207.6±9.2** (104)	150.32±1.0 (101)
30	245.35±7.6** (216)	246.48±2.8** (152)	212.57±3.8** (109)	207.16±18.3** (103)	152.2±0.6 (102)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100%, **P<0.01

Table 3: The serum potassium levels (mmol/l) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg), aspirin (100mg/kg), or vehicle. Serum levels were measured before (zero hours) and after administration of drugs on given hours.

Hours	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	5.05±0.29 (100%)	5.93±0.17 (100%)	3.36±0.23 (100%)	3.8±0.14 (100%)	5.42±0.24 (100%)
1	5.33±0.2** (106)	6.36±0.1* (107)	3.84±0.2** (114)	4.33±0.1* (114)	5.42±0.2 (100.0)
2	5.56±0.2** (110)	6.85±0.1** (116)	4.06±0.3** (121)	4.82±0.0** (127)	5.42±0.3 (100)
4	5.80±0.2** (115)	7.18±0.2** (121)	4.33±0.2** (129)	5.31±0.0** (140)	5.37±0.3 (99)
6	5.95±0.2** (118)	7.5±0.2** (127)	4.51±0.2** (134)	5.70±0.1** (150)	5.40±0.2 (100)
8	6.11±0.2** (121)	7.80±.1** (132)	4.63±0.2** (138)	5.92±0.1** (156)	5.45±0.2 (101)
10	6.31±0.2** (125)	8.08±0.1** (136)	4.81±0.1** (143)	6.09±0.1** (160)	5.40±0.3 (100)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100%, * P<0.05, **P<0.01

Table 4: The serum Potassium levels (mmol/l) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg), aspirin (100mg/kg) or vehicle. Serum levels were measured before (zero hours) and after two hours of administration of drugs on given days.

Days	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	5.05±0.29 (100%)	5.93±0.17 (100%)	3.36±0.23 (100%)	3.8±0.14 (100%)	5.42±0.24 (100%)
5	5.45±0.2* (108)	6.3±0.1* (106)	4.28±0.2* (127)	3.80±0.2** (100)	5.5±0.2 (101)
10	6.75±0.4* (134)	6.18±0.1* (104)	4.98±0.2 (148)	4.56±0.2* (120)	5.52±0.2 (102)
15	8.55±0.3** (169)	6.45±0.1* (109)	4.93±0.0** (147)	5.40±0.3* (142)	5.62±0.2 (104)
20	7.73±0.2** (153)	5.96±0.2 (101)	4.44±0.2** (132)	5.13±0.2* (135)	5.77±0.2 (107)
25	7.33±0.2** (145)	6.18±0.2 (104)	4.95±0.1* (147)	5.81±0.3* (153)	5.52±0.2 (102)
30	6.95±0.2* (138)	7.23±0.2** (122)	4.94±0.1* (147)	6.34±0.2* (167)	5.62±0.3 (104)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100%
* P<0.05, **P<0.01

(table 6) phase of the study presented a significant (P<0.05; P<0.01) increase while, animals whom vehicle was administered showed no change in the parameter. Serum creatinine concentration was also significantly (P<0.01) raised by the four drugs in an identical fashion in both acute (table 7) and chronic (table 8) studies, however vehicle-treated group of animals did not exhibit any effect on this parameter.

DISCUSSION

The data shows that diclofenac Na^+ and K^+ significantly maintained raised serum electrolyte levels, while alminoprofen and aspirin after initial increase returned to pretreatment values and showed a similar response. These data are in compliance with previous findings by Mahboob and Haleem (1989). Contrarily, diclofenac

Table 5: The serum urea levels (mg/dl) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg), aspirin (100mg/kg) or vehicle. Serum levels were measured before (zero hours) and after administration of drugs on given hours.

Hours	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	35.20±0.8 (100%)	36.84±0.73 (100%)	34.05±2.63 (100%)	33.55±1.39 (100%)	29.80±1.0 (100%)
1	36.28±0.8** (103)	37.73±0.5** (103)	37.01±2.5 (109)	37.33±2.4* (110)	29.70±1.0 (99)
2	37.90±0.7** (108)	38.11±0.5** (104)	38.68±2.8* (114)	38.39±2.4* (114)	30.04±0.8 (101)
4	38.35±0.8** (109)	38.73±0.5** (105)	39.45±2.7* (117)	39.27±2.5* (117)	29.75±0.9 (100)
6	38.9±0.7** (111)	39.46±0.6** (107)	40.27±2.6* (119)	40.72±2.6* (121)	29.72±0.9 (100)
8	40.35±0.6** (115)	40.03±0.6** (109)	41.53±2.8* (123)	42.64±2.4** (127)	29.83±1.0 (100)
10	41.76±0.4** (120)	40.91±0.4** (111)	43.37±2.9* (128)	43.18±2.5** (128)	29.94±1.2 (100)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100%,
* P<0.05, **P<0.01

Table 6: The serum urea levels (mg/dl) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg) aspirin (100mg/kg), or vehicle.Serum levels were measured before (zero hours) and after two hours of administration of drugs on given days.

Days	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	35.20±0.8 (100%)	36.84±0.73 (100%)	34.05±2.63 (100%)	33.55±1.39 (100%)	29.80±1.0 (100%)
5	52.83±0.8** (151)	48.66±2.2** (132)	41.11±2.3* (123)	39.06±1.0** (117)	33.81±1.2 (112)
10	60.55±0.5** (173)	59.70±1.0** (162)	55.72±4.8 (164)	43.25±1.1** (130)	33.01±1.7 (112)
15	63.68±0.5** (182)	69.08±0.9** (188)	51.69±3.9** (152)	63.55±1.2** (191)	32.67±1.3 (110)
20	83.53±0.8** (238)	68.84±1.0** (188)	54.96±3.2** (161)	60.55±1.2** (182)	32.26±1.5 (110)
25	61.23±0.6** (175)	57.69±0.6** (157)	62.73±3.1** (184)	56.46±0.9** (170)	32.55±1.9 (111)
30	57.35±0.4** (163)	56.41±0.6** (154)	54.93±1.6** (161)	52.47±1.2** (158)	31.06±1.3 (104)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100%
* P<0.05, **P<0.01

sodium has been reported to cause an insignificant change in sodium levels even seven post-treatment days (Besen *et al*., 2009). These findings are in agreement to the data in rabbits (Mahboob and Haleem, 1989), whereas Bensen *et al*., (2009) did not report any increase after administration of diclofenac sodium. The current data also show that both diclofenac salts have almost similar effect on Na and K concentrations, which might not present any clinical advantage of these drugs to each other. The data is in compliance with previous studies indicating renal toxicity induced by NSAIDS (Marasco *et al*., 1987; Shield, 1993; Segal *et al*., 2006). In contrast, studies conducted in patients also showed insignificant elevation in renal functions after administration of NSAIDS (Jelić-Ivanović *et al*., 1985; Bonney *et al*., 1986).

Table 7: The serum creatinine levels (mg/dl) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg), aspirin (100mg/kg), or vehicle. Serum levels were measured before (zero hours) and after administration of drugs on given hours.

Hours	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	2.16±0.09 (100%)	2.03±0.06 (100%)	1.7±0.06 (100%)	1.65±0.09 (100%)	1.72±0.16 (100%)
1	2.49±0.1* (116)	2.73±0.1** (134)	2.06±0.0 (121)	1.95±0.7 (119)	1.84±0.1 (107)
2	2.77±0.0** (129)	3.36±0.1** (165)	2.26±0.0* (133)	2.13±0.0 (131)	1.84±0.1 (109)
4	3.0±0.1** (139)	3.93±0.1** (193)	2.41±0.0** (142)	2.41±0.0** (148)	1.87±0.0 (112)
6	3.33±0.1** (155)	4.76±0.1** (235)	2.56±0.0** (151)	2.76±0.0** (169)	1.95±0.1 (115)
8	3.58±0.1** (167)	5.05±0.1** (249)	2.71±0.0** (159)	3.31±0.1** (204)	1.84±0.1 (109)
10	4.09±0.1** (190)	5.48±0.2** (271)	2.90±0.0** (171)	3.60±0.1** (220)	1.81±0.1 (107)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100%
* P<0.05, **P<0.01

Table 8: The serum creatinine levels (mg/dl) of rabbits that have received either diclofenac sodium, diclofenac potassium (2.5mg/kg), alminoprofen (10mg/kg), aspirin (100mg/kg) or vehicle. Serum levels were measured before (zero hours) and after two hours of administration of drugs on given days.

Days	Diclofenac sodium	Diclofenac potassium	Almino-profen	Aspirin	Control
0	2.16±0.09 (100%)	2.03±0.06 (100%)	1.7±0.06 (100%)	1.65±0.09 (100%)	1.72±0.16 (100%)
5	3.16±0.1** (147)	5.33±0.1** (263)	2.03±0.0 (119)	4.23±0.1** (256)	1.87±0.1 (110)
10	2.83±0.1* (132)	4.31±0.1** (213)	2.51±0.1* (148)	3.88±0.1** (235)	1.9±0.1 (111)
15	2.35±0.1 (109)	4.5±0.1** (222)	2.26±0.4** (133)	2.76±0.1** (167)	1.9±0.1 (113)
20	2.28±0.2** (106)	2.95±0.1** (146)	2.26±0.4** (133)	3.18±0.1** (193)	1.9±0.1 (111)
25	2.83±0.1** (131)	2.55±0.1** (126)	2.25±0.1** (132)	2.7±0.0** (164)	1.75±0.1 (102)
30	2.46±0.1 (115)	2.41±0.1** (119)	2.85±0.0** (168)	2.46±0.1* (149)	1.9±0.1 (112.)

Each value presents Mean ± S.E.M (mmol/l) (n=6)
Values in parentheses present % increase or decrease in serum concentration considering the zero hour value as 100%
* P<0.05, **P<0.01

CONCLUSION

Current findings support earlier evidence of renal function impairment with administration of NSAIDs, however this study could not find an advantage of diclofenac potassium over diclofenac sodium on electrolyte levels of experimental animals in either acute or chronic phase of treatment.

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