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The effect of tiaprofenic acid on blood pressure control in treated hypertensive patients

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Summary

Eleven patients with osteoarthritis and mild hypertension completed an 8-week, double-blind crossover study in which 200 mg tiaprofenic acid 3-times daily or placebo were substituted for their normal non-steroidal anti-inflammatory therapy. Systolic blood pressure was significantly higher on tiaprofenic acid therapy than on placebo and plasma renin activity was significantly lower on active treatment. No significant changes were seen in biochemical parameters, though the weight of the patient was also higher on tiaprofenic acid than on placebo. Duration of morning stiffness was also lower on tiaprofenic acid than on placebo. Blood pressure on tiaprofenic acid was not different from baseline readings on other non-steroidal anti-inflammatory drug therapy. This study suggests that tiaprofenic acid, like other non-steroidal anti-inflammatory agents, may interfere with blood pressure control in treated hypertensive patients.

Key words: Tiaprofenic acid - analgesics, anti-inflammatory - antihypertensives - osteoarthritis - hypertension

Introduction

Tiaprofenic acid† is a new non-steroidal anti-inflammatory drug which has significant anti-inflammatory and analgesic effects in animal models of inflammation.[5] Pharmacokinetic studies demonstrate rapid absorption from the gastro-intestinal tract with a relatively short plasma elimination half-life of about 2 hours.[13] Treatment for 2 weeks failed to demonstrate any significant accumulation or alteration in biotransformation.[4] A number of short-term controlled clinical trials conducted in patients with rheumatoid arthritis and osteoarthritis [1, 16, 20] have

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demonstrated the anti-inflammatory and analgesic activity of the drug. Tiaprofenic acid, therefore, would seem to be a useful addition to the currently available range of non-steroidal anti-inflammatory drugs.

Tiaprofenic acid like other non-steroidal anti-inflammatory drugs inhibits platelet cyclo-oxygenase but does not seem to inactivate the lipoxygenase pathway.[15] Prostaglandins also appear to play a major role in the control of blood pressure, acting either as vasodilators[9] or through modulation of renin release.[6,7] Recently, a number of non-steroidal anti-inflammatory agents have been shown to increase blood pressure in treated and untreated hypertensive patients. Indomethacin has been shown to interfere with the acute effects of captopril,[19] oxprenolol[14] and a variety of other antihypertensive medications.[18]

In view of the common use of non-steroidal anti-inflammatory drugs in elderly patients who may well also be on antihypertensive medications, we decided to examine the effects of tiaprofenic acid on blood pressure control in treated hypertensive patients using a double-blind randomized placebo controlled trial.

Patients and methods

Twelve patients with osteoarthritis of the hip or the knee who required non-steroidal anti-inflammatory drug therapy and who were being maintained on antihypertensive medication were selected from those attending the Out-Patient Department and admitted to the study. There were 7 males and 5 females aged between 55 and 74 years (mean 62 years). All had a supine diastolic blood pressure that had been less than 110 mmHg during the previous 3 months. Antihypertensive medication and non-steroidal anti-inflammatory drug treatment had remained unchanged and blood pressure had been stable and well controlled during this 3-month period. Details of the medication they had been receiving are given in Table I.

The trial was of 8-weeks' duration with two 4-week treatment periods of either 200 mg tiaprofenic acid 3-times daily or identical placebo given 3-times daily. Patients were allocated to the treatments in a random order and changed directly from their previous non-steroidal anti-inflammatory drug therapy on to tiaprofenic acid or placebo at the commencement of the study. At the end of the first 4-week treatment period they were crossed over to the alternative medication for a further 4 weeks.

If added analgesia was required during the study, 15 to 30 mg codeine phosphate orally was taken. Antihypertensive therapy was maintained unchanged during the 8 weeks of treatment.

Patients attended the clinic at weekly intervals for measurement of blood pressure, heart rate, weight and clinical measures of joint disease activity. Supine and standing systolic and diastolic (Phase IV and V) blood pressures were recorded by the same observer on each occasion using a random zero sphygmomanometer and an ordinary mercury sphygmomanometer. The same blood pressure machines were used throughout the study. Clinical measures of disease activity (pain scores on activity and at night, and duration of morning stiffness on a 10 cm visual analogue scale) were also made by the same observer on each occasion. At the end

Table I. Details of previous non-steroidal anti-inflammatory drug and antihypertensive therapy in the patients studied

Patient No.	Non-steroidal anti-inflammatory		Antihypertensive		Treatment group
	Drug	Daily dose	Drug	Daily dose	
1*	Sulindac	400 mg	Propranolol	120 mg	Placebo/active
			Bendrofluazide	5 mg	
2	Naproxen	500 mg	Prazosin	2 mg	Placebo/active
			Metoprolol	300 mg	
			Bendrofluazide	5 mg	
3	Diflunisal	500 mg	Atenolol	50 mg	Active/placebo
			Hydrochloro-thiazide	50 mg	
			Amiloride	5 mg	
4	Naproxen	500 mg	Pindolol	20 mg	Active/placebo
			Frusemide	40 mg	
5	Naproxen	500 mg	Chlorthalidone	25 mg	Active/placebo
	Diflunisal	250 mg			
6	Diclofenac	150 mg	Methyclothiazide	25 mg	Placebo/active
7	Ibuprofen	800 mg	Chlorthalidone	25 mg	Placebo/active
8	Naproxen	500 mg	Pindolol	10 mg	Active/placebo
9	Sulindac	200 mg	Timolol	15 mg	Active/placebo
10	Piroxicam	20 mg	Propranolol	40 mg	Active/placebo
11	Indo-methacin	100 mg	Methyldopa	500 mg	Placebo/active
			Methyclothiazide	5 mg	
12	Sulindac	200 mg	Methyldopa	500 mg	Placebo/active
			Hydrochloro-thiazide	50 mg	
			Amiloride	5 mg	

*Withdrew at end of Week 1 (on placebo) because of severe increase in pain

of each 4-week treatment period, plasma samples were obtained for the measurement of electrolytes, urea and creatinine concentration, plasma renin activity (PRA)[2] and aldosterone concentrations (PAC).[12] On the last day of each treatment period, a 24-hour urine sample was collected for measurement of daily electrolyte excretion.

All values were expressed as the mean (±S.E.M.) and comparisons between the two treatment periods (tiaprofenic acid and placebo) for each parameter were made using a Student's t-test for paired values. Regression analysis was also carried out on the data to assess the effect of treatment order.

Results

One patient dropped out of the study on the fourth day because of a failure of placebo to control the joint symptoms, but 11 patients completed the study.

The results of the study are summarized in Table II where the mean values for the 11 patients of the clinically measured parameters at the end of the 4-week treatment period on tiaprofenic acid and on placebo are given.

Comparing blood pressure data at the end of each 4-week treatment period, it

Table II. Measurements of blood pressure and clinical parameters of osteoarthritis at the end of 4-weeks' treatment with tiaprofenic acid or placebo: mean (±S.E.M.) values for 11 patients

Measurement	Placebo	Tiaprofenic acid	Comparison		Regression analysis		
			t	p	Tiaprofenic acid effect	z	p
Supine blood pressure (mmHg)							
Random zero sphygmomanometer:							
Systolic	127±3	137±4	−2.48	<0.025	11.46	2.38	<0.05
Diastolic							
(Phase IV)	86±2	88±2	−0.81	N.S.	3.34	0.99	N.S.
(Phase V)	81±2	84±2	−1.01	N.S.	4.06	1.25	N.S.
Mercury sphygmomanometer:							
Systolic	129±3	135±4	−1.77	N.S.	10.06	2.27	<0.05
Diastolic							
(Phase IV)	89±2	90±2	−0.68	N.S.	1.74	0.62	N.S.
(Phase V)	85±2	85±2	−0.16	N.S.	1.02	0.36	N.S.
Standing blood pressure (mmHg)							
Random zero sphygmomanometer:							
Systolic	123±2	136±2	−3.58	<0.005	16.98	3.67	<0.01
Diastolic							
(Phase IV)	89±3	97±2	−2.07	<0.05	8.72	2.60	<0.02
(Phase V)	84±3	92±2	−1.92	<0.05	8.04	2.37	<0.05
Mercury sphygmomanometer:							
Systolic	126±3	136±3	−3.02	<0.01	8.48	1.64	N.S.
Diastolic							
(Phase IV)	92±3	96±2	−0.68	N.S.	4.30	1.12	N.S.
(Phase V)	88±3	91±2	−0.97	N.S.	4.38	1.18	N.S.
Clinical parameters of osteoarthritis							
Pain score:							
Activity	4.5±0.8	4.5±1.0	0.19	N.S.	−1.28	−1.54	N.S.
At night	3.1±0.5	3.5±0.9	0.53	N.S.	−1.22	−1.83	N.S.
Duration of morning stiffness: visual analogue score	2.1±0.3	1.8±0.2	1.55	N.S.			

N.S.=not significant

can be seen that blood pressure was slightly higher for all measurements on tiaprofenic acid compared to placebo but the difference only reached statistical significance for some values. No clinical effects of this increased blood pressure were noted during the short duration of the study. Regression analysis showed that the blood pressure in patients on tiaprofenic acid was not significantly different from pre-treatment values when patients were receiving other non-steroidal anti-inflammatory drugs and that blood pressure on placebo was lower than that measured when patients were on previous non-steroidal therapy.

Plasma renin activity at the end of the tiaprofenic acid phase was 0.28±0.26 ng/ml/hr as compared to 0.95±0.54 ng/ml/hr on placebo, while plasma aldo-

sterone was 6.3±2.9 ng/100 ml on tiaprofenic acid as opposed to 7.9±5.2 ng/100 ml on placebo. No significant changes were seen in biochemical parameters or in serum or urinary electrolyte concentrations over the duration of the study.

Pain score both at night and on activity measured on a 10 cm visual analogue scale were not significantly different between placebo and tiaprofenic acid. The duration of morning stiffness was less during the tiaprofenic acid phase than during placebo.

Discussion

Interactions between non-steroidal anti-inflammatory and antihypertensive agents have been demonstrated in a number of previous studies[14,17-19] but have not been reported previously with tiaprofenic acid.

The present study has demonstrated statistically significant differences in blood pressure of mildly hypertensive osteoarthritic patients treated with tiaprofenic acid or placebo. These patients had previously been on a variety of antihypertensive agents and non-steroidal anti-inflammatory agents, as shown in Table I. Blood pressure tended to decrease during the placebo phase and to return to pre-treatment levels, i.e. those measured when patients were on previous non-steroidal anti-inflammatory drug therapy during the tiaprofenic acid treatment period. Although a significant increase in blood pressure was only noted in one of the measurements, there was a trend towards increased blood pressure on active treatment for all measurements. However, the increase in blood pressure was only slight and it was difficult to assess the clinical significance of this increase. In this study, the effect of tiaprofenic acid seemed to be independent of the particular hypertensive regimen used, which is again in keeping with previous studies.[11,18]

The mechanism of this interaction is unclear, although it has been postulated that non-steroidal anti-inflammatory drugs will reduce the formation of arachidonic acid metabolites having potential hypertensive and natriuretic effects.[10] It has also been suggested by Watkins *et al.*[17] that the increased blood pressure seen during non-steroidal antihypertensive therapy may be due to sodium retention. No differences were noted in urinary electrolyte excretion between the placebo and tiaprofenic acid phases, but weight was noted to be slightly greater during the tiaprofenic acid treatment period. No changes were seen in plasma creatinine during the tiaprofenic acid phase, a feature that has been described with some other non-steroidal anti-inflammatory drugs.[3,8]

Disease activity in these patients with mild osteoarthritis was not significantly different during placebo or active treatment periods, and this may well reflect that these patients had little active inflammatory joint disease likely to respond to non-steroidal anti-inflammatory drug therapy at the time of entry to the trial. It is interesting to note that the duration of morning stiffness measured on a 10 cm visual analogue scale did increase from 1.8 to 2.1 cm during the placebo phase, but did not change during the active treatment period.

In conclusion, blood pressure has been shown to be slightly higher in treated hypertensive patients during tiaprofenic acid therapy than during placebo. The blood pressure measured on tiaprofenic acid, however, was not significantly

different from that on previous non-steroidal anti-inflammatory drug therapy. The mechanism of this interaction is unclear but may be related to inhibition of prostaglandin synthesis and care, therefore, should be taken in hypertensive patients being treated with tiaprofenic acid as with other non-steroidal anti-inflammatory agents.

References

1. Berry, H., Bloom, B., and Hamilton, E. B. D., (1982). A dose ranging study of tiaprofenic acid in osteoarthritis. *Rheumatology*, **7**, 118-124.
2. Bonin, J. M., Cain, M. D., Jose, J. S., Mukherjee, T. M., Perrett, L. V., Scroop, G. C., and Seymour, A. E., (1977). Hypertension due to a renin-secreting tumour localised by segmental renal sampling. *Aust. N.Z. J. Med.*, **7**, 630-635.
3. Brooks, P. M., and Cossum, P., (1978). Salicylates and creatinine clearance re-evaluated. *Aust. N.Z. J. Med.*, **8**, 660-661.
4. Camp, A. V., (1981). Tiaprofenic acid in the treatment of rheumatoid arthritis. *Rheumatol. Rehabil.*, **20**, 181-183.
5. Deraedt, R., Benzoni, J., and Delevallee, F., (1982). Pharmacological profile of tiaprofenic acid. *Rheumatology*, **7**, 78-87.
6. Gerber, J. G., Olson, R. D., and Nies, A. S., (1981). Inter-relationship between prostaglandins and renin release. *Kidney Int.*, **19**, 816-821.
7. Henrich, W. L., (1981). Role of prostaglandins in renin secretion. *Kidney Int.*, **19**, 822-830.
8. Henrich, W. L., (1983). Nephrotoxicity of non-steroidal anti-inflammatory agents. *Am. J. Kidney Dis.*, **11**, 478-484.
9. Horton, R., Zipser, R., and Fichman, M., (1981). Prostaglandins, renal function and vascular regulation. *Med. Clin. North Am.*, **65**, 891-914.
10. Lee. J. B., (1977). Prostaglandins, neutral lipids, renal, interstitial cells and hypertension. In: "Hypertension". Eds.: J. Genest, E. Koiw and O. Kuchel. McGraw Hill. New York.
11. Mills, E. H., Whitworth, J. A., Andrews, J., and Kincaid-Smith, P., (1982). Non-steroidal anti-inflammatory drugs and blood pressure. *Aust. N.Z. J. Med.*, **12**, 478-482.
12. Ogihara, T., Iinuma, K., Nishi, K., Arakawa, Y., Takagi, A., Kurata, K., Miyai, K., and Kumahara, Y., (1977). A non-chromatographic non-extraction radio immunoassay for serum aldosterone. *J. Clin. Endocrinol. Metab.*, **45**, 726-731.
13. Pottier, J., Cousty-Berlin, D., and Busigny, M., (1982). Human pharmacokinetics of tiaprofenic acid. *Rheumatology*, **7**, 70-77.
14. Salvetti, A., Arzilli, F., Beggi, P., and Motolese, M., (1982). Interaction between oxprenolol and indomethacin on blood pressure in essential hypertensive patients. *Eur. J. Clin. Pharmacol.*, **2**, 197-201.
15. Schrör, K., Neuhaus, V., Ahland, B., Sauerland, S., Kuhn, A., Darius, H., and Bussmann, K., (1982). Actions of tiaprofenic acid on vascular prostacyclin biosynthesis and thromboxane and 12-HPETE formation of human platelets *in vitro* and *ex vivo*. *Rheumatology*, **7**, 88-98.
16. Thompson, M., Daymond, T. J., Essigman, W. K., Huskisson, E. C., and Wojtulewski, J. A., (1982). Short-term efficacy and tolerance of tiaprofenic acid ('Surgam') in rheumatoid arthritis and osteoarthritis: multi-centre, placebo controlled trials. *Curr. Med. Res. Opin.*, **8**, 215-223.
17. Watkins, J., Abbott, E. C., Hensby, C. N., Webster, J., and Dollery, C. J., (1980). Attenuation of hypotensive effect of propranolol and thiazide diuretics by indomethacin. *Br. Med. J.*, **281**, 702-705.
18. Wing, L. M. H., Bune, A. J. C., Chambers, J. P., Graham, J. R., and West, M. J., (1981). The effects of indomethacin in treated hypertensive patients. *Clin. Exp. Pharmacol. Physiol.*, **8**, 537-541.
19. Witzgall, H., Hirsch, F., Scherer, B., and Weber, P. C., (1982). Acute hemodynamic and hormonal effects of captopril are diminished by indomethacin. *Clin. Sci.*, **62**, 611-615.
20. Wojtulewski, J. A., Walter, J., and Thornton, E. J., (1981). Tiaprofenic acid (Surgam) in the treatment of osteoarthritis of the knee and hip. *Rheumatol. Rehabil.*, **20**, 177-180.