ROLE OF PROSTAGLANDIN SYNTHESIS INHIBITORS IN THE PASSAGE OF URETERIC CALCULUS

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ABSTRACT

Diclofenac sodium, one of the prostaglandin synthesis inhibitors was evaluated in terms of passage or movement of ureteric stones upto the size of 0.5 cm in a series of 80 patients. Forty-six (57.5%) patients passed the stone within a period of 4 weeks. This frequency of stone passage was significantly higher when compared with stone passage of similar size in other series (P< 0.001). In 17(56.6%,) out of 30 patients, stone moved from upper and middle ureter to the lower ureter which is also significant from therapeutic point of view. Complete pain relief was achieved in 67 (84%) patients. No side effects of the drug noted in this series. The sequence of events following ureteral obstruction by the stone, based on recent experimental and clinical diclofenac sodium was highlighted (JPMA 41: 268,1991).

INTRODUCTION

Renal colic caused by ureteral obstruction by a stone is one of the most common emergency situation in surgical practice in our country requiring urgent and prompt relief. The aims of the treatment in this situation are urgent and complete relief of pain, to prolong the pain free interval between the pain episodes and adopt measures which enhance the passage of stone. The efficacy of prostaglandin synthesis inhibitors like indomethacin and diclofenac sodium has been established in the treatment of renal colic[1], but their exact role in facilitating the passage of ureteric stones is not yet clear. The purpose of this study is to evaluate the efficacy of diclofenac sodium in the passage of ureteric stones.

MATERIALS AND METHODS

Eighty patients of both sex, above the age of 15 years, having radiopaque ureteral stones with transverse diameter between 0.3-0.5cm were included in this study. Excluded from this study were, (a) patients having stones above a ureteral stricture, due to congenital anomalies and stones associated with severe hydronephrosis requiring urgent relief, (b) patients having history of hypersensitivity reaction to drugs, peptic ulcer, asthma, cardiac failure, hepatic failure, renal impairment and blood coagulation disorders, (c) pregnant women and lactating mothers, and (d) patients who experienced nausea or vomiting due to the acute colic. All patients had complete clinical evaluation, urine examination, complete blood picture, blood urea, serum creatinine and plain X-ray abdomen and pelvis to see the side, site and size of the stone. Renal ultrasonography was done in all cases to see the dilatation of upper urinary tract and intravenous urography only in selected patients. All the patients were given diclofenac sodium tablets in doses of 100 mg each twice daily for two weeks. The patients were followed at 2 and 4 weeks. On each follow-up, patients were asked about the passage of stone and relief of pain as complete, partial or no relief. Plain X-ray abdomen and pelvis was taken in each case to confirm the passage or movement of stone by comparing it with the previous X-ray. Upper urinary tract dilatation was monitored by ultrasonography. Statistical analysis was done by comparingthe frequency of stone passage in this study with spontaneous passage of stone in another study12 using Chi-Square test.

RESULTS

The present study was carried out from 1st November, 1988 to 30th September, 1989. The age and sex distribution is shown in the Table.

TABLE. Age and Sex distribution.

AGES	MALE	FEMALE	TOTAL
15 - 19	3	1	4
20 - 29	18	8	26
30 - 39	21	3	24
40 - 49	9	4	13
50 - 59	7	0	7
60 - 69	3	2	5
70 - 79	0	1	1
Total	61	19	80

Duration of symptoms varied between one day and 5 years. Of 80 patients included in this study, 77(96%) had renal pain, one had backache, one painless haematuria and one patient presented with pain at the tip of the penis. Other associated symptoms were gross haematuria in 13 patients and burning micturation in 8 patients. Previous history of renal pain varying from 2 months to 8 years was noted in 9, haematuria in one, passage of stone in 7 and operation for upper urinarytract stone disease in 2 cases. Family history of upper urinary tract stone disease was present in 8 patients. Urinalysis showed microscopic haematuria in 19 patients. Blood urea and serum creatinine were within the normal range in all patients. Stones were present in the right ureterin 37(46.25%) and left ureter in 43 (53.75%) patients. Plain X-ray of abdomen and pelvis on the first visit showed stone in the upper ureter in 24 (30%), middle ureter in 6 (7.5%) and lower ureter in 50(62.5%) patients. The size of the stone along the transverse diameter was 0.5 cm in 45 patients, 0.4 cm in 26 and 0.3 cm in 9 patients. Renal ultrasonography of the affected kidney showed mild hydronephrosis in 25 patients and moderate hydronephrosis in another 13 patients. Following drug therapy 46(57.5%) patients passed the stone. Thirty-nine (78%) out of 50 patients, passed the stone from the lower ureter, 3 (50%) out of 6, from the middle ureter and 4 (16.6%) out of 24, from the upper ureter. The stone moved from the upper and middle ureter in 17 (56.6%) out of 30 patients. In 16 patients the stone has moved from the upper ureter to the lower ureter and in one from middle to the lower ureter. When stone passage was related to the size of the stone, 22 (49%) of 45 patients passed 0.5 cm stone, 19 (73%) of 26 patients 0.4 cm stones and 5(55%) of 9, 0.3cm stones. The pain relief was complete in 67 (84%) and partial in 13 (16%) patients. Out of 46 patients who passed stones, only 12 were able to retrieve the stone. On analysis 9 (75%) had pure calcium oxalate and 3 (25%) mixed (calcium oxalate and uric acid) stones. No side

effect of the drug was noted by any of the patients in this series.

DISCUSSION

Following acute unilateral ureteral obstruction by stone, there is a sudden rise in the intrapelvic pressure[3]. This is due to the stagnation of urine proximal to the ureteral stone. This high intrapelvic pressure stimulates the release of prostaglandin E2 (PGE2) from the renal medulla[4]. Prostaglandin E2 increases blood flow to the kidney by causing reduction in the afferent arteriolar resistance[5,6]. The increased blood flow to the kidney leads to the Increase in the glomerular filtration rate. The increased ifitration rate in the face of ureteral obstruction further elevates the intrapelvic pressure. Furthermore, prostaglandin E2 induces diuresis by counteracting the action of antidiuretic harmone on the renal tubules[7]. The diuresis in combination with increased glomerular filtration rate further elevate the intrapelvic pressure. In addition, the obstructing ureteral stone causes inflammation and oedema at the site of impaction, by producing local inflammatory mediators including prostaglandins[8]. This local inflammation and oedema increase the mechanical obstruction at the site of stone impaction resulting in further elevation of intrapelvic pressure. It has been suggested that increased intrapelvic pressure leads to high tension in the pelvic and ureteral wall muscles. This high tension keeps the stone attached to the ureteral wall thus hampering its descent. The efficacy of prostaglandin synthesis inhibitors, in term of lowering the intrapelvic pressure has been proved in experimental studies[9,10] and in clinical trials for the relief of renal colic[1,2]. These agents lower the intrapelvic pressure by inhibiting the release of prostaglandins. They combat the inflammation and oedemaat the site of the stone impaction. In addition, they relax the pelviureteral wall smooth muscles by inhibiting the prostaglandins, as prostaglandins cause contraction of these muscles[11]. These effects of the prostaglandin synthesis inhibitors were the basis to perform a clinical trial to evaluate these agents in facilitating the passage of ureteral stones and our present study with diclofenac sodium attests the value of these agents. Of course, a clinical drug trial in ureteral stones is difficult because the incidence of spontaneous passage is high and use of placebo drug is unethical because of associated renal colic which has to be relieved by some effective drug. The overall success rate, regarding stone passage in our patients treated with diclofenac sodium is much higher if we compare our results with the previous studies of spontaneous passage of ureteral stones. In our study of 80 patients stone passage was noted in 46 (57.5%) patients. Fox et al[12] have shown spontaneous stone passage in 89 (30.5%) of 292 cases treated over a period of 5 years. In this series, all but five cases had stones smaller than 0.3 cm in diameter and stone passage was achieved over a period of 12 months. On the other hand, in our series all except nine had diameter greater than 0.3 cm and 57.5% passed stone over a period of four weeks following drug therapy. Even then when result of our series were compared with this series using Chi-Square test, the difference was highly significant ($P < 0.001$). The frequency of stone passage in other series[13-16] varied from 28 to 43 percent. Statistical comparison with these series was not possible because the stone size was not mentioned. In addition, in 17 (56.6%) out of 30 patients, the stones moved from the upper-half to the lower-half of the ureter in our series. This movement of stone is significant because, stone which has moved from the upper ureter to the lower ureter, has a better chance of passage, if given time and the treatment of stones in the lower ureter by ureterorenoscopy, has a much higher success rate and a lower complication rate than in the upper ureter. Holmlund[17] has studied the effect of oxyphenbutazone on the passage of stone less than 4 mm size. Twenty four out of 41 in the treated group and 5 out of 29 in control group, passed the stone. The difference was statistically significant ($P< 0.001$). Similar results were reported using oxyphenbutazone by Nygard and Bjorneby[18]. In another study[19] when meglumine indomethacinate (Liometacen) was used the passage of ureteric stone was noted in 15 (48.4%) out of

31 patients whereas 12, only (16%) out of 75 patients, passed stone when methamizol was used. The difference was statistically significant ($P < 0.001$). These studies[17-19] and the present series show the efficacy of antiinflammatory drugs in the treatment of ureteric stones.

REFERENCES

1. Holmlund, D. and Sjodin, J.G. Treatment of ureteral colic with intravenous indomethacin. 3. Urol., 1978;120:676.
2. Khalifa, M.S. and Sharkawi, M.A.Treatmentof pain owing to acuteureteral obstruction with prostaglandin synthetase inhibitor: A prospective randomized study. 3. Urol., 1986;136:393.
3. Gottschalk, C.W. and Mylle, M. Micropuncture study of pressure in proximal tubules and peritubular capillaries of the rat kidney and their relation to ureteral and renal venous pressures.Am. J. PhysioL, 1956;185:430.
4. Olsen, U.B., Magnussen, M.P. and Eilertsen, E. Prostaglandinus, a link between renal hydro and hemodynamic in dogs. Acta. Physiol. Scand., 1976;97:369.
5. Navar, L.G. and Baer, P.G. Renal autoregulatoryand glomerular filtration responses to gradated ureteral obstruction. Nephron., 1970;7:301.
6. Vaughan, E.D. Jr., Shenasky, J.R. and Gillenwater, J.Y. Mechanism of acute haemodynarnic response to ureteral occlusion. Invest. UroL, 1971;9:109.
7. Grantbam, 3.3. and Orloff, J. Effect of prostaglandin-E1 on thesodium transportandon the permeability response of the isolated collecting tubule to vasopressin, adenosin 3' 5',.monophosphate and theophylline. J. Clin. Invest., 1968;47:1154.
8. Holmlund, D. Ureteral stones: An experimental and clinical study of the mechanism of the passage and arrestof ureteral stones. Scand. J. UroL NephroL, 1968; Suppl. 1.
9. Sjodin,J.G. and Holmlund, D.E.W. Effects of saline load, roentgencontrastmediumsnd indomethacin ondiuresis and pelvicpressure in the acuteobstructed kidney. Br. J. UroL, 1982;54:446.
10. Sjodin, 3.0., Wahlberg. J. and Persson, A.E.G. The effect of indomethacin on glomerular capillary pressure and pelvic pressure during ureteral obstruction. J. UroL, 1982;127:1017.
11. Cole, R.S., Fry, C.H. and Shuttleworth, K.E.D. The action of the prostaglandins on isolated human ureteric smooth muscle. Br. 3. UroL, 1988;61:19.
12. Fox, M., Pyrab, L.N. and Raper, F.P. Management of ureteric stone; a review of 292 cases. Br.J. Urol., 1965;37:660.
13. Henry, H.H. and Tomlin, E.M. Ureteral calculi: Review of 17 years of experience at a community hospital. 3. IJroL, 1975;113:762.
14. Prince, C.L and Scardino, P.L A statistical analysis of ureteral calculi. 3. Urol., 196083:561.
15. Mahon, F.B. Jr. and Waters, R.F. Acritical reviewof stone manipulation; a5.yearstudy. 3. Urol., 1973;110:387.
16. Kittredge, W.E. and James, D. Management of ureteral calculi. 3. Urol., 1954;72:342,
17. Holmlund, D. Oxyphen-butazone in the treatment of acute ureteral stone disease. Scand. 3. UroL Nepbrol., 1968; suppl. 1:63.
18. Nygard, A. and Bjorneby, S. Oxyphenbutazone in the treatment of acute ureteral stone disease. Scand. J. UroL Nephrol., 1975;9:36.