THE ROLE OF PROSTAGLANDINS IN THE LOWER URINARY TRACT DYNAMICS OF PROSTATECTOMIZED PATIENTS: A TRIAL WITH INDOMETHACIN AND ASPIRIN

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SUMMARY

Using 49 prostatectomized patients as experimental subjects, we studied the effects of indomethacin and acetylsalicylic acid — accredited prostaglandin synthetase inhibitors — from a urodynamic and clinical standpoint. Relevant urodynamic data was gathered 1 hr 30 min after the patients had taken the drugs and placebo. Clinical results were further scrutinized after 8 days of treatment, at which time a new urodynamic workup was again performed on some patients. Results were again studied shortly after the end of treatment. The effect of the drugs on bladder and urethral structures was borne out by clear-cut clinical and urodynamic changes. After statistically analyzing such changes, we concluded that prostaglandin synthesis inhibition resulting in the inhibition of prostaglandin action had, at least in part, led to the changes noted. In the present report we shall discuss the role played by the highly complex mechanisms at work.

INTRODUCTION

Research has already been carried out in vitro and in experimental animals in order to determine the effect of prostaglandins on bladder and urethral structures. The causes behind possible synthesis stimuli and activating mechanisms of bladder and urethral structures have been the subject of several papers. Only very spotty work has been done, nevertheless, on human beings in vivo.

Our clinical study and thorough urodynamic research project, which began in 1979, had as its aim the better understanding of the role of prostaglandins in normal and pathological vesico-sphincteric dynamics. The patients chosen as the target group of our study had all undergone open surgery for benign hypertrophy of the prostate. Since such patients often display vesico-urethral dysfunctions and exhibit a posterior urethra simplified and reduced to the distal sphincters, the study of changes undergone in this area would be easier to chart.

Changes brought about by the synthesis inhibition of endogenous prostaglanins and related substances provided us with the data we needed for our study. To effect the desired result, we used two drugs, indomethacin and aspirin, which despite their total chemical dissimilarity, both inhibit prostaglandin synthesis. The study of accumulated experimental and clinical data provided us with the dosage of both drugs (sufficient to completely inhibit the synthesis of prostaglandins and related substances) and the spacing of administrations.
MATERIAL AND METHODS

59 patients were chosen on the basis of strict clinical, radiological and laboratorial criteria. When necessary, an I.V.P. was performed. Retrograde and micturition cystourethrograms were done on all patients and an endoscopy was performed whenever the presence of an organic lesion was suspected. When confirmed, the patient was excluded. Also excluded were patients with diabetes, neurological or psychiatric disorders, persistent organic bladder neck and urethral obstructions, total sphincteric incontinence, and those operated for simultaneous vesical lesions. The use of indomethacin and aspirin led us to rule out patients with gastroduodenal ulcers as well. Patients were not allowed to take any other type of medication starting at least a week before and during the period of the trial.

A three-month post-operative time lapse was considered the minimum necessary for the probable eradication of residual inflammation and the epithelization of the area operated on. Given our interest in studying the clinical effects of our therapy we tried to bring together all patients we could suffering from functional disorders, that become rarer after that time period.

A pre-operative and current clinical picture of each case was formed, using a clinical protocol that helped us to place the patients in two categories: normal (asymptomatic) with 16 cases, and those suffering from a variety of functional disturbances — 43 cases. The patients were then divided into three main groups: placebo group with 12 patients, 8 of whom later became part of the indomethacin group which had 47 cases in all, and 4 of whom later joined the aspirin group composed of 12 cases.

At the onset of our trial all patients underwent a urodynamic work-up listed on Table 1, in which the terminology used is shown. A Disa (R) system was used. Urethral pressure profiles were not performed. International Continence Society recommendations, terminology, units and symbols were used whenever possible. The procedure followed in each urodynamic work-up and a few details not clearly included in International Continence Society reports need to be described.

With the patient supine, after having passed urine, a 12F polyethylene urethral catheter was introduced under local anesthesia and residual urine was measured. The bladder was then filled at a continuous rate of approximately 2 ml s⁻¹ with a room temperature normal saline solution. In 39 cases, pressures (cm H₂O) were measured, with a suprapubic 5 F polyethylene catheter and in the remaining cases with a 6 F polyethylene urethral catheter. Abdominal pressure was measured using a rectal latex baloon catheter. Detrusor pressures were indirectly obtained, by subtracting abdominal from intravesical pressures. Maximum abdominal and detrusor pressures were not measured. Detrusor post-micturition contraction pressure was obtained as indicated for the other detrusor pressures.

The slope's to the limit and collagen segment, when detectable were mathematically analysed (cm H₂O per 100 ml), as prescribed by Merrill et al and graphically represented. The same values which were directly measured on the intravesical pressure curve, were used to calculate the compliance in the muscular and collagen phases of bladder filling and are expressed in ml for cm H₂O.

To detect possible detrusor instability provocative stimuli such as coughing, standing and heel jouncing were employed during this phase.
Micturition pressures and flow (ml s⁻¹) were then studied and either intermittent (I) or continuous (C) patterns of the flow were noted along with cases of terminal dribble (D).

Urethral resistance (units) was measured using the formula:

\[
\text{Intravesical pressure at maximum flow} \div (\text{Maximum flow rate})^2
\]

The relationship between pressure (intravesical and detrusor, at maximum flow) and maximum flow was analysed using the guidelines established by Abrams and Torrens, Griffiths and adopted by the International Continence Society. The relationship was then depicted on graphs.

At the end of micturition, residual urine was again measured and figures confirmed by subtracting voided volume from maximum cystometric capacity.

External sphincter electromiography was performed on all patients.

The work-up was repeated 1 hr. 30 min. after the administration of placebo (12 cases), 150 mg of indomethacin in capsules (47 cases), or 2.000 mg of aspirin in tablet form (12 cases). The placebo administered, it may be added, was identical in appearance to the drug to be taken by the patient later on, when participating in the indomethacin or aspirin groups.

In the next stage, patients with clinical disturbances were singled out for 8 days of treatment, sufficient time for reliable results but not long enough to permit the natural tendency of this kind of patients to improve to significantly impair the conclusions. A placebo was administered to 12 patients (who between a week and a month later became part of the other two groups), 50 mg of indomethacin, 3 times per day at approximate 8 hour mealtime intervals to 32 patients; or 1.000 mg of aspirin, 3 times a day at 8-hour mealtime intervals, to 9 patients. After 8 days were over, a fourth group was formed with 5 patients from the indomethacin group. These patients underwent another identical urodynamic work-up in order to note any further changes that may have taken place.

Finally, doctors (unaware of what the patients had been given) analysed all placebo, aspirin and indomethacin patients with clinical disturbances, after the 8 days were over, in order to note any changes in symptoms.

Of the 41 patients submitted to therapy for clinical disturbances (indomethacin-32; aspirin-9), we succeeded in contacting 27 (indomethacin-23; aspirin-4) between 15 and 45 days after the end of therapy, and were thus able to gather more useful information regarding the further evolution of symptoms in each case.

Clinical changes and urodynamic alterations were compared with the results gathered from studying the placebo group.

The subjective nature of symptoms, the variability of their frequency in each group, the sparceness of certain symptoms as a whole, and the need to qualify some results by grading them, thus avoiding the all or nothing approach, led us to prefer the presentation of clinical results without a statistical analysis. Thus, changes noted are expressed in terms of percentages.

The uniformity of all 4 groups at the start was checked statistically using the Student's t test, based on urodynamic figures, obtained before medication had been given.

Urodynamic alterations underwent a statistical paired t test analysis since the patients functioned as their own control. The graphs presented, show the means and standard error of the means.

The following symbols were used on the graphs, depending on statistical significance:

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>0.05</td>
<td>P</td>
</tr>
<tr>
<td>0.01</td>
<td>P</td>
</tr>
<tr>
<td>0.001</td>
<td>P</td>
</tr>
</tbody>
</table>

The Fischer and Yates table was used.

It is important to stress that both clinical and urodynamic results were analysed within each group through comparison of the results obtained before and after the administration of the drugs or placebo. We did not attempt to compare the groups; the placebo patients were used to give us an

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TABLE 1. Urodynamic terminology.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abdominal</th>
<th>Detrusor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-micturation pressure</td>
<td>Pves,pm</td>
<td>Pabd,pm</td>
</tr>
<tr>
<td>Opening pressure</td>
<td>Pves,op</td>
<td>Pabd,op</td>
</tr>
<tr>
<td>Maximum pressure</td>
<td>Pves,max</td>
<td>Pabd,max</td>
</tr>
<tr>
<td>Pressure at maximum flow</td>
<td>Pves,Qmax</td>
<td>Pabd,Qmax</td>
</tr>
<tr>
<td>Contraction pressure at maximum flow</td>
<td>Pdet,pm</td>
<td></td>
</tr>
<tr>
<td>Post-micturation contraction</td>
<td>Pdet,op</td>
<td>Pdet,Qmax</td>
</tr>
<tr>
<td>Urethral Resistance</td>
<td>Pdet,pm</td>
<td></td>
</tr>
<tr>
<td>Good pressure</td>
<td>Pdet,op</td>
<td></td>
</tr>
<tr>
<td>Opening time</td>
<td>Pdet,Qmax</td>
<td></td>
</tr>
<tr>
<td>Vv</td>
<td>Pdet,op</td>
<td></td>
</tr>
<tr>
<td>Qm</td>
<td>Pdet,Qmax</td>
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</tr>
</tbody>
</table>

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idea of the natural evolution of the situation independent of the action of drugs and under the influence of the instrumentation for the urodynamic study.

RESULTS

Our findings showed that patients subjected to the influence of indomethacin and aspirin experienced a clinical improvement in symptoms that was not apparent in the placebo group (Table 2). The fact that there was larger number of subjects in the indomethacin group than in the aspirin group undoubtedly conditioned results obtained. Although improvement of some symptoms was more noticeable in the former group, the general tendency was the same in both groups. Initial disturbances tended, for the most part, to reappear after the end of treatment, although slight improvement was maintained in some cases (Table 3).

Urodynamic values obtained, shown in detail in Fig. 2 to 10 and Table 4, exhibit several statistically significant variations caused by both drugs and not by the placebo. The variation of values on the 8th day under indomethacin was similar and in certain aspects even more pronounced than at 1 hr. 30 min. The smaller number of patients who took part in the 8th-day group prevents us from drawing any definite conclusions.

<table>
<thead>
<tr>
<th>TABLE 2. Symptom changes in 53 patients subjected to the influence of placebo, indomethacin and acetylsalicylic acid.</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>a)</td>
</tr>
<tr>
<td>Diurnal interval of micturitions (n = 2)</td>
</tr>
<tr>
<td>b)</td>
</tr>
<tr>
<td>Number of micturitions per night (n = 6)</td>
</tr>
<tr>
<td>False desire to void (n = 3)</td>
</tr>
<tr>
<td>Urgency (n = 1)</td>
</tr>
<tr>
<td>Stress incontinence (n = 2)</td>
</tr>
<tr>
<td>Urge incontinence (n = 2)</td>
</tr>
<tr>
<td>Terminal dribbling (n = 1)</td>
</tr>
<tr>
<td>Initial delay (n = 1)</td>
</tr>
<tr>
<td>Straining (n = 1)</td>
</tr>
<tr>
<td>Stream: - calibre (n = 2)</td>
</tr>
<tr>
<td>- strength (n = 4)</td>
</tr>
<tr>
<td>TENESMUS (n = 1)</td>
</tr>
<tr>
<td>Sensation of bladder fullness after micturition (n = 6)</td>
</tr>
<tr>
<td>Burning on micturition (n = 4)</td>
</tr>
</tbody>
</table>

It should be noted that the variation in parameters for asymptomatic cases was identical to those which showed clinical disturbances. It is important to stress that the correlation between clinical and urodynamic data was frequently poor upon first inspection. Some symptoms frequently associated with instability were not detectable on the urodynamic curve, even under provocative tests. The opposite was also true. In two patients, uninhibited contractions were present in the complete absence of symptoms, a phenomenon noted by other investigators. The correlation between clinical and urodynamic data was much clearer with regard to micturition phenomena.
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Fig. 2 — Slope

Fig. 3 — Compliances (Intravesical Pressure)
The summarized analysis of graphs showing urodynam-ic results using a placebo and indomethacin and aspirin shows that the prostaglandin synthesis inhibitors brought about a decline in the slope (Fig. 2) (especially in the tonus limb), increase in muscular compliance, (Fig. 3) delay in first sensation and increase in bladder capacity (Fig. 4). Insta-
tability disappeared in only a limited number of cases (21.3% in the indomethacin group). In cases in which instability was still present, after medication, we noted pressure variations in the contractions which proved to be non signifi-cant when analysed statistically, (Fig. 5).

Greater ease in the onset of micturition, patent in shorter opening time, (Fig. 6), and lower intravesical opening pressure (Fig. 7A,B,C, and D), was apparent, as was greater ease in the process of micturition as a whole. Maximum and average flow rates improved, (Fig. 8), with interrupted streams becoming continuous in some cases (6 in the indomethacin group and 1 in the aspirin group) (Table 4). One of the most noteworthy changes was in terminal dribble, which decreased in all cases submitted to medication (Tables 2 and 4). Urethral resistance decreased (Fig. 9) and pressure flow relationship improved (Fig. 10). In cases where it was present, residual urine decreased (Fig. 4) thus showing improved bladder emptying. Improved flow and vesic- 
al emptying were characterized by an overall drop in micturition pressures (maximum intravesical pressure and intravesical pressure at maximum flow) (Fig. 7A,B,C and D). Post-micturition detrusor contraction suffered non-signifi- 
cant variations (Fig. 7A,B and C).

Side effects were infrequent with both drugs and their intensity slight enough to have been considered unimpor-
tant by the patients.

Fig. 4 — First desire to void, maximum and effective cystometric capacities, voided volume and residual urine

Fig. 5 — Instability

Fig. 6 — Opening time, time to maximum flow and voiding time
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Fig. 7 — A, B, C, D. Micturition Pressures
Fig. 8 — Maximum and average flow rates

Fig. 9 — Urethral resistance
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Fig. 10 — Pressure-flow relationships

TABLE 4. Flow variations during urodynamic study.

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>Acetylsalicylic acid</th>
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<tbody>
<tr>
<td></td>
<td>1h 30m (n = 47)</td>
<td>1h 30m (n = 12)</td>
</tr>
<tr>
<td></td>
<td>8 days (n = 5)</td>
<td></td>
</tr>
<tr>
<td>Q1 → QC</td>
<td>(n = 8) 75%</td>
<td>(n = 1) 100%</td>
</tr>
<tr>
<td>QD → —</td>
<td>(n = 2) 100%</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

Two chemically dissimilar drugs — indomethacin and aspirin — known to be potent prostaglandin synthesis inhibitors since Vane's pioneer study,\textsuperscript{88} were used in our trial. Though we allowed the possibility that these NSAID (non-steroidal anti-inflammatory drugs) can act directly on certain structures through mechanisms that are still poorly understood,\textsuperscript{32,33,34,35,46} it is our opinion that the changes in bladder and urethral dynamics we noted, were at least partly due to the synthesis inhibition of prostaglandins which through complex mechanisms act on specific receptors.\textsuperscript{32,76}

The dosage of the drugs, the spacing between administrations, and the analysis of main urodynamic results (1 hr, 30 min.) were based on pharmacological knowledge and previous studies using prostaglandin synthesis inhibitors.\textsuperscript{33,24} Consultation of other sources\textsuperscript{12,13,21,62,75,88} leads us to believe, with little margin of doubt, that the inhibition of prostaglandin and related substances (tromboxanes) was probably complete in all cases.

Frequent relapse after the end of treatment was taken as further substantiation of the fact that good results were probably due to the action mentioned. Inhibitor action is known to be practically immediate,\textsuperscript{22,52} and since the tissues do not store prostaglandins to any significant degree, it is clear that synthesis inhibition represents an inhibition of the effects.\textsuperscript{68,69,90,98} Given this fact, it is likely that inhibitors such as indomethacin and aspirin, will only show any significant action during the actual period of administration.

We must not disregard the possible effect of the drugs on central or peripheral sensitivity.\textsuperscript{48,71,99,100} and this might well have been prostaglandin synthesis inhibition as well.\textsuperscript{26,102} This effect could have had a complementary action on bladder and urethral structures thus contributing to the improvement of certain symptoms such as burning upon micturition, sensation of bladder fullness after micturition, delay of first sensation with consequent decrease of frequency of micturitions, and decrease of bladder sensitivity, (a possible factor of increased capacity of the organ). We know however that the pressure at which the micturition reflex is triggered is the pre-micturition pressure. Since the micturition reflex appeared when greater bladder capacities were brought about but under lower pre-micturition pressures, it is logical to suppose that local muscular or neuromuscular action was predominant over a possible depressive action on the sensitive sphere.

The analysis of the results in the filling and micturition phases showed us that both prostaglandin synthetase inhibitors brought about diffuse and non-specific muscle relaxation.

Contrary to Ruch's findings\textsuperscript{72} the absence of any decline in the slope for our placebo group (which, in fact exhibited some statistically non-significant increase (Fig. 2)), makes it clear that the distension of the bladder caused by the pre-medication examination was not a factor in slope decline in patients submitted to the drugs. Bladder hypertonus, probably due to muscular hypertrophy from pre-operative obstruction and sometimes patent in high pressures, could be ascribed, at least to a certain degree, to prostaglandins. Decrease in bladder hypertonus, caused by the inhibitors, would thus be easy to understand. Slope figures obtained by us were generally higher than those mentioned by Merriil et al.\textsuperscript{49} This was taken as an indicator of hypertonus of purely muscular origin found in somewhat hypertonic bladders and detachment of detrusor action in the filling phase is known to be non-neural.\textsuperscript{67,72,80} Thus, it is likely that factors affecting the detrusor during this phase were of a direct muscular nature.

We know that several stimuli affect prostaglandins synthesis,\textsuperscript{18,22,31,32,51,57,58,59,70,73} among them is bladder distension.\textsuperscript{28,31} Thus, it is altogether possible that prostaglandin production may be increased in cases like ours. Besides the mentioned direct muscular action, tissue reaction to neuro-transmitters may be altered by higher prostaglandin levels, which would influence neurovegetative action.\textsuperscript{36,37,39,43}

Muscle relaxation caused by the drugs, affected predominantly those muscles that make up the intrinsic distal sphincteric mechanism.\textsuperscript{17,47} The presence of relaxation of these muscles (the only functional ones in the posterior urethra of a prostatectomized patient) would be the only feasible explanation for improved flows and emptying where low intravesical pressures are present.

Decrease in micturition pressures was probably due both to a direct action on the detrusor whose sensitivity to prostaglandin action is experimentally proved,\textsuperscript{2,5,12,52} and to the decrease brought about in urethral resistance. It is a known fact that a decrease in intravesical pressure is a normal consequence of better urethral permeability.

The relaxation of urethral musculature mentioned, which is responsible for continence in prostatectomized patients,\textsuperscript{14} was taken as the cause of heightened sphincteric incontinence.

Cases of clinically and urodynamically detected obstruction that improved with treatment were attributed to a probable hypertonic intrinsic striated sphincter.\textsuperscript{79,80,86} Countereacted by the medication given, which, as experiments have proved possible, acted directly on muscular function.\textsuperscript{2,5,12,52,67} Some improvement may also be ascribed to more complex and difficult-to-analyse neuro-muscular mechanisms.\textsuperscript{52,60,66}

Fig. 1 shows the structures on which the prostaglandins had to act in order to cause the changes described. Ghoneim et al.\textsuperscript{69} found that the detrusor distension releases PGE$_2$, which, when inhibited by indomethacin, does not exercise its relaxing effect on the urethra. Our experience demonstrated a different effect, since we obtained a relaxing effect on the urethral muscles with the prostaglandin synthetase inhibitors. If we keep the multiple and frequently opposing actions of all prostaglandins in mind, it is easy to understand the different results obtained. Analysis of pertinent bibliography\textsuperscript{2,5,12,52,67} only seems to demonstrate the difference between the results obtained by several investigators. Since PGE$_2$ contracts the urethral muscles\textsuperscript{53,57} while PGE$_3$ relaxes them,\textsuperscript{5,28,65} it is obvious that the results noted will depend on which prostaglandin is acting at any given moment.

The correlation between clinical and urodynamic factors, unclear when first approached, became obvious when we analysed the improvement of symptoms from the standpoint of the urodynamic changes found. These changes, though non-specific (appearing identical in asymptomatic cases and those with clinical disturbances alike), were obviously responsible for countereacting those physiopathological mechanisms behind the clinical dysfunctions we found.

Instability, a poorly understood phenomenon,\textsuperscript{26,83} underwent changes detected in our urodynamic study. These changes though minor, are considered by us to be noteworthy, given the generally poor results obtained with even the most aggressive types of treatment.\textsuperscript{56,84,85} The decrease in urethral resistance may have had an influence on the improvement.\textsuperscript{58,86} It is important to stress that even to the most astute observer, there often seems to be no correlation between certain symptoms such as frequency, urge incontinence, etc., and urodynamic instability. This occurs not only upon first approach but also when trial results are analysed. With the use of indomethacin and aspirin, improvement of
symptoms was more frequent than improvement of instability in the urodynamic study.

Some authors do not distinguish between long post-micturition detrusor contractions, which obviously do not show up in normal urodynamic studies and those very short-acting post-micturition contractions, detectable in these studies. The former type of contraction is a possible cause of certain symptoms such as sensation of bladder fullness after micturition. Both types are detrusor contractions and possibly signify instability. The causes of these contractions have been widely interpreted. In our cases, the short-acting, urodynamically detectable form was encountered less frequently than by other authors30, and changes resulting from the use of the drugs proved to be contradictory and inconclusive.

The marked improvement in micturition efficacy easily explained the improvement of symptoms such as poor stream, hesitancy, etc., we obtained in our cases.

Improvement of terminal dribbling, which some investigators associated with instability, was ascribed to improved emptying of the bladder and a decrease in intravesical pressure after micturition.

The knowledge we have about the complex action of prostaglandins on physiological and pathological phenomena is still very incomplete. This information gap prevents us at this time from delving deeper into the discussion of precise mechanisms involved in the vesico-sphinisteric changes found in our cases.

Up to now, little research has been done into the relationship between prostaglandins and lower urinary tract dynamics — a field that opens up whole new realms of possibilities for the treatment of vesico-sphinisteric dysfunctions.

It is our hope that this project, to our knowledge the first to be done on human subjects in vivo, will provide the stimulus for further research into this necessary, yet relatively unexplored field.

References


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