Measurement of Prostate-Specific Antigen and Prostatic Acid Phosphatase Concentrations in Serum before and 1–42 Days after Transurethral Resection of the Prostate and Orchidectomy

Alun Price, Stephen E. A. Attwood, John B. F. Grant, Trevour A. Gray, and Kenneth T. H. Moore

Preoperative intra-individual variation for determinations of prostate-specific antigen and prostatic acid phosphatase concentrations, 15–30% in 92 patients with benign prostatic hyperplasia, limits the diagnostic usefulness of both tumor markers. In benign prostatic hyperplasia (214 patients), concentrations of these tumor markers increased in the initial postoperative period. Prostatic acid phosphatase concentration then decreased by the third postoperative day. Prostate-specific antigen concentration remained above normal in the first postoperative week but had decreased by 42 days. In prostatic carcinoma (46 patients), the concentrations of these tumor markers did not increase postoperatively. During the first week, the concentrations of prostatic acid phosphatase began to fall, but prostate-specific antigen showed a decrease only at 42 days. After orchidectomy (11 patients), the concentrations of both markers had decreased by five days. Concentrations of prostate-specific antigen but not of prostatic acid phosphatase were significantly increased in patients with metastases at 42 days postoperatively. When the concentration of tumor marker did decrease, the magnitude of change was greater for prostatic acid phosphatase than for prostate-specific antigen. These changes were accentuated after an orchidectomy.

Additional Keyphrases: benign prostatic hyperplasia - tumor markers

Prostate-specific antigen (PSA), a glycoprotein belonging to the serine protease group (1–3), is produced only in the prostatic ductal epithelium (4). The physiological role of PSA is liquefaction of seminal fluid (3). Serum PSA concentrations measured before prostatectomy are increased both in patients with prostatic carcinoma and in those with benign hyperplasia (5–7). Prostatic acid phosphatase (PAP; EC 3.1.3.2) is essential for maintaining normal spermatid metabolism.

Both proteins are in current use as tumor markers for prostatic carcinoma. Results of previous studies of PSA concentration in patients with this disease suggest that the test may be useful in screening for carcinoma (8), in directing the preoperative diagnosis (9–13), in monitoring the progression of established disease (10, 12, 14–16), and in monitoring the response to therapy (13, 17–22). In transurethreal resection of benign prostatic hyperplasia, most of the adenoma is removed, whereas in transurethral resection of prostatic cancer, removal of tissue is limited to that required to relieve obstruction of outflow from the bladder. In our hospital, radical prostatectomy is not performed. Variation in the amount of tissue removed and the loss of hormonal stimulation of the prostate after an orchidectomy complicate the assessment of the perioperative concentrations of PSA and PAP.

We undertook a prospective study to establish the pattern of change of PAP and PSA concentrations in serum directly after transurethral prostatectomy (TURP) in patients with prostatic carcinoma and benign hyperplasia. Our aim was to document changes in the serum concentrations of these tumor markers, to improve interpretation of follow-up sampling, and to evaluate whether these changes could be used to distinguish between benign and malignant disease.

Materials and Methods

Patients: All patients who presented to the Urology Department in a 12-month period and in whom a prostatectomy or orchidectomy was planned were included in the study. The patients were divided into three groups: those with benign hyperplasia treated by TURP, those with carcinoma treated by TURP alone, and those with carcinoma treated by orchidectomy (and no TURP). Patients treated by TURP had an obstruction of bladder outflow. Patients having an orchidectomy had clinical symptoms of already diagnosed prostatic carcinoma, established either by needle biopsy or by a TURP done at least three months before the orchidectomy. Patients who underwent both TURP and orchidectomy within three months were excluded from the study. Diagnosis of malignancy was made by histological examination of the resected prostatic tissue or, in the case of those patients undergoing an orchidectomy alone, by needle biopsy. The presence of bony metastases was established by isotope bone scan.

Sample collection: We collected 10 mL of venous blood from all patients on the day before the operation and one, three, five, and 42 days after the operation. All samples were taken in the morning and before any digital examination of the prostate. A second preoperative sample was obtained from 92 of the patients with benign prostatic hyperplasia.

Tumor marker assays: PAP was measured by radioimmunoassay (Du Pont UK Ltd., Stevenage, Herts, UK).
Results

Table 1 shows the range of concentrations of each marker before surgery. For both proteins, the serum concentration is significantly (P < 0.001) higher in patients with malignant disease than in those with benign disease, but the range of values shows considerable overlap between the groups. Table 2 shows the percentage of patients in each group in whom the concentrations of the markers are below the upper limit of normal as defined by the kit manufacturers; also shown is the percentage with serum PSA <10 µg/L, a value suggested to be the best discriminator between prostatic carcinoma and benign hyperplasia (II) and recommended as a useful operational cutoff value by Hybritech in their product literature. No similar discriminative cutoff value has been recognized for PAP.

As Table 2 demonstrates, PSA is increased in more patients than PAP and the concentration of PAP decreases at a faster rate than PSA concentration in both benign and malignant prostatic disease. The necessity of waiting until the first postoperative visit to assess tumor marker concentration is self-evident.

Of the patients with benign disease, 92 (34%) had two or more blood samples taken before their TURP. We used the results from these samples to construct an intra-individual precision profile (23) for PSA and PAP (Figure 1). There were too few data points to extend the profile to higher concentrations or to construct one for patients with malignant disease. Therefore, we drew no conclusions concerning the intra-individual variation of PSA and PAP in patients with prostatic cancer.

The concentrations of PAP and PSA before and after TURP are shown in Figure 2. Table 3 summarizes the significance of any changes from preoperative to postoperative concentrations.

Table 1. Range of PSA and PAP Concentrations in Benign Prostatic Hyperplasia (BPH) and Prostatic Carcinoma (PC)

<table>
<thead>
<tr>
<th></th>
<th>PSA</th>
<th>PAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BPH</td>
<td>PC</td>
</tr>
<tr>
<td>Maximum</td>
<td>150</td>
<td>1591</td>
</tr>
<tr>
<td>90th centile</td>
<td>16</td>
<td>99</td>
</tr>
<tr>
<td>Median</td>
<td>8.0</td>
<td>25</td>
</tr>
<tr>
<td>10th centile</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>&lt;0.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Meta, metastatic disease.

Table 2. Percentage of Patients on Each Day with Tumor Marker Concentrations below the Cutoff

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>Cutoff limit</th>
<th>Pre</th>
<th>+1</th>
<th>+3</th>
<th>+6</th>
<th>+42</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>&lt;4</td>
<td>34</td>
<td>7.6</td>
<td>9.6</td>
<td>18.6</td>
<td>67</td>
</tr>
<tr>
<td>PSA</td>
<td>&lt;10</td>
<td>68</td>
<td>34</td>
<td>42</td>
<td>57</td>
<td>95</td>
</tr>
<tr>
<td>PAP</td>
<td>&lt;3.3</td>
<td>51</td>
<td>21</td>
<td>70</td>
<td>77</td>
<td>83</td>
</tr>
</tbody>
</table>

Malignant cases

| PSA          | <4           | 4.3 | 2.9 | 3.3 | 7.4 | 17.5 |
| PSA          | <10          | 17  | 11  | 20  | 18.5| 32.5 |
| PAP          | <3.3         | 19  | 23  | 60  | 40  | 40  |

* Upper limit of reference range quoted by kit manufacturers.

Fig. 1. Intra-individual precision profile of PAP and PSA

Patients with Benign Disease

The concentrations of both markers significantly increased in the first postoperative day (P <0.001). By the third postoperative day, the PAP concentration showed a significant decrease (P <0.005), and was still decreased on day 42, at which time 83% of these patients had PAP concentrations within the reference range. PSA tended to decrease in the first five days postoperatively, but the decrease was not statistically significant. By day 42, PSA concentrations were close to reference values, although 33% of these patients still had PSA concentrations above the upper limit of the reference range.

Patients with Prostatic Carcinoma

Neither marker showed an initial increase postoperatively. PAP showed no statistically significant change.
We therefore compared changes as a ratio to the preoperative concentrations in those patients for whom we had data at days 1, 3, and 5 (for benign prostatic hyperplasia, n=70; prostatic carcinoma TURP, n=27; prostatic carcinoma orchidectomy, n=6). The median ratios are shown in Figure 4.

After a TURP, the ratio of pre- and postoperative PSA concentrations was greater in patients with prostatic cancer than in those with benign hyperplasia at days 1 (P<0.001), 3 (P<0.01), and 5 (P<0.05), whereas the relative change in PAP concentration was greater only on the first day after surgery but decreased significantly (P<0.02) by day 3 and maintained this decrease at day 42. There was no postoperative fall in PSA concentration during the first five days but at day 42 the PSA concentration had decreased significantly (P<0.002).

In patients with deposits visible on bone scan, on day 42 the concentration of PSA but not of PAP was significantly (P<0.01) greater than in patients without evidence of metastases (Figure 3).

Patients undergoing an orchidectomy had higher values for both markers preoperatively than those patients with prostatic cancer undergoing a TURP (P<0.05). Both PSA and PAP concentrations showed a significant decrease by the fifth postoperative day; they were further decreased by day 42, at which time the concentrations of the tumor marker did not differ significantly from those in patients undergoing TURP alone for malignant disease.

Because the intra-individual variation was so large and because we had only three data points per subject, we could not produce half-life data for the immediate postoperative period.

![Fig. 2. Effect of TURP and orchidectomy on PAP concentration in (left to right): patients with benign disease, patients with malignant disease, patients with malignant disease who also had an orchidectomy. The number of patients in each group is shown in parentheses. P = pre-operative concentration. +1, +3, +5, and +42 are concentrations at 1, 3, 5, and 42 days post-operation. —, median; ☐, interquartile range; ——, absolute range.]

![Fig. 3. Effect of TURP and orchidectomy on PSA concentration in (left to right): patients with benign disease, patients with malignant disease, and patients with malignant disease who also had an orchidectomy. Symbols as in Fig. 2.]

![Fig. 4. Concentrations of PSA and PAP at 42 days post-operative in patients who did (●) or did not (○) have metastatic deposits on bone scan.]

**Table 3. Significance of Changes in PSA and PAP Concentrations Relative to Preoperative Values**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of days post-turp</th>
<th>PAP</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 3 5 42</td>
<td>1 3 5 42</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>I* Dc Dc Dc</td>
<td>I* I* I* Dc</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>NS Dc Dc Dc</td>
<td>NS NS NS Dc</td>
<td></td>
</tr>
<tr>
<td>Orchidectomy</td>
<td>NS NS Dc Dc</td>
<td>NS NS Dc Dc</td>
<td></td>
</tr>
</tbody>
</table>

I* = increase, D* = decrease, NS = not significant. * P<0.001, b P<0.002, c P<0.005, d P<0.01, e P<0.02, f P<0.05.
at day 1 (P <0.001). At days 1, 3, and 5 after an orchidectomy, the post/preoperative PSA concentration was lower (P <0.02) than in prostatic cancer patients who did not have an orchidectomy, whereas the relative change in PAP concentration was lower (P <0.05) only at days 3 and 5. Comparison of their post/preoperative ratios showed no significant difference between PAP and PSA at day 1; but at days 3 and 5, PSA concentrations were relatively higher than PAP concentrations in patients with benign hyperplasia (P <0.001) or with prostatic carcinoma, even after an orchidectomy (P <0.05). Essentially, when there was a decrease in tumor marker concentration after TURP, the magnitude of the change was greater for PAP than PSA. These changes were even greater after an orchidectomy.

**Discussion**

Use of reference ranges derived from men without urological disease is inappropriate if applied to patients having benign prostatic hyperplasia. For distinguishing between benign hyperplasia and prostatic cancer, it is also inappropriate to take a cutoff value that was derived in one specific population of patients and apply it to a different population. Examination of Table 2, which shows how unhelpful cutoff values for PSA and PAP are for categorizing patients with prostatic disease, it is hoped will discourage such practices. Individual hospitals should establish their own cutoff values by receiver-operator-characteristic analysis (24) of their own population with its unique incidence of prostatic carcinoma and benign prostatic hyperplasia. Such an analysis of our preoperative population yielded optimal discrimination at values of 16 µg/L for PSA (true-positive rate 79%, false-positive rate 21%) and 4.5 µg/L for PAP (true-positive rate 71%, false-positive rate 33%).

Preoperative concentrations of PSA and PAP do not accurately predict the presence of prostatic carcinoma because of the significant overlap with marker concentrations in benign hyperplasia. This is, in part, attributable to the biological variation of serum PAP and PSA concentrations, which range from 15% to 30%. This estimate is higher than the 3.1–9.4% found by Schifman et al. (25) for PSA but similar to their 7.5–48.5% for PAP and similar to the 17.6% for PSA and 51.5% for PAP found by Dejter et al. (26). The differences for PSA may be explained by the fact that the data from Schifman et al. came from 10 patients with prostatic carcinoma, whereas in our study we used 92 patients with benign hyperplasia. Also the mean PSA concentrations were 112 µg/L in the study of Schifman et al. vs 7 µg/L for the 92 patients here. Our intra-individual precision profile shows a decrease with increasing concentration so it is possible that the intra-individual CV is lower at higher PSA concentrations. Thus, in symptomatic patients, the use of these markers to assess malignancy preoperatively is limited.

The half-life of PSA has been determined as 53 h for patients with benign prostatic hyperplasia (9) and 75 h for patients with cancer confined within the prostatic capsule (12). Because TURP removes PAP- and PSA-producing tissue, the concentration of each in serum will decline to a new steady-state that reflects the PAP and PSA produced from metastatic site(s) or from any remaining prostate tissue. A long half-life for either tumor marker could thus reflect malignant and possibly metastatic disease. The effects of surgery differ in patients with benign and malignant disease. Serum concentrations of both markers increase in the first postoperative day in patients with benign disease. This increase may be due to manipulation of the gland during surgery and may reflect the effect of irrigating fluid being absorbed into the bloodstream through the prostatic veins. We saw no significant increase in serum concentrations of the markers after TURP of patients with prostatic carcinoma. Although similar quantities of PSA and PAP are entering the blood, the higher initial values seen in malignant disease might mean that the increase in concentration is proportionately much smaller than in benign disease and hence more difficult to detect. In addition, the distal metastases would not be affected by surgery and thus would continue to secrete marker into the bloodstream.

The large decrease in circulating PSA by day 42 post-orchidectomy indicates that hormone manipulation significantly affects the behavior of the malignant cell, just as it does the secretory activity of the normal prostate (27). The new steady-state value 42 days after the operation provides a baseline that may allow detection of any subsequent progress of the disease. The failure of orchidectomy to reduce PSA or PAP concentrations to within the reference range reflects the fact that orchidectomy reduces the metabolism of all the prostatic tissue but does not necessarily eradicate all the malignant cells (28, 29).

PSA and PAP both show large intra-individual variation, which limits their diagnostic usefulness before resection. Also, after the operation, extensive multiple sampling would be required to produce accurate data on the diagnostic significance of tumor-marker half-life in patients with benign and malignant prostatic disease. Such multiple sampling would be expensive for routine.

![Fig. 5. Changes in PSA and PAP concentrations relative to preoperative concentrations in patients with benign prostatic hyperplasia ●, prostatic cancer ○, TURP or orchidectomy ▼](image_url)
testing. Because the concentration of PSA and PAP may be increased after the operation, assessment of the concentration of the tumor markers should be delayed until the subject’s first visit as an outpatient.

Many thanks to Dr. G. Owen for his encouragement of this work.

References