PIVKA-II concentrations in patients with cystic fibrosis

Montaletbem et al report that PIVKA-II was detected in 33% of patients with cystic fibrosis, while vitamin K, plasma concentrations were normal.1 It is astonishing that deficiencies of vitamin K in patients with cystic fibrosis,2 PIVKA-II was detectable in these patients. The authors conclude that PIVKA-II is not associated with vitamin K deficiency, but with the use of antibiotics.

There is some doubt as to whether the assay for PIVKA-II used by the authors is reliable. Widdershoven et al compared different methods for measuring PIVKA-II and reported that techniques involving adsorption of normal factor II may result in false positive values, because the carboxylated prothrombin may not be removed completely.3 Determination of PIVKA-II by monoclonal antibody was found to be the most specific and sensitive method.4 We did not detect PIVKA-II in any of eight patients with cystic fibrosis who were supplemented with vitamin K (4-30 mg/day).1 In only one of the unsupplemented patients with cystic fibrosis was PIVKA-II found (0.16 AU/ml). This patient took antibiotics, but a low vitamin K, concentration of 0.06 μg/ml and a Thrombostet of 56%.2 The authors do not mention the vitamin K concentration for PIVKA-II, hence there is no information on concentrations of vitamin K, it is impossible to establish normal values for vitamin K, PIVKA-II, however, is a direct reflection of the availability of total vitamin K in the liver and hence is associated with vitamin K deficiency. In our study PIVKA-II was found in only one unsupplemented patient with cystic fibrosis, and hence we conclude that vitamin K deficiency occurs infrequently in cystic fibrosis.5

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5 Lefrère JJ et al comment:

Dr Lefrère et al comment:

Our PIVKA-II assay, based on the activity of staphylococcalurease, is widely used in many laboratories. The results obtained with this procedure for those of laboratories measuring PIVKA-II by monoclonal antibody, in particular in patients with hepatocellular carcinoma. Furthermore, we measured PIVKA-II concentrations in a large population of healthy individuals (blood donors) and obtained no false positive result in these individuals.

Dr Cornilissen et al do not raise the possibility of increased PIVKA-II in contexts other than vitamin K deficiency, such as hepatocellular carcinoma,6,6 hepatoblastoma,7 effect of oral anticoagulants and cephalosporins.8 Indeed, vitamin K deficiency is not the only mechanism to generate PIVKA-II. In hepatocellular carcinoma increased PIVKA-II concentration is probably due to an acquired enzymatic anomaly which disturbs the γ-carboxylation of all vitamin K dependent factors.9 We could not explain this increase in our patients with cystic fibrosis and without vitamin K deficiency. This increase might have been linked to the interference of certain drugs on the enzymatic system of γ-carboxylation of vitamin K dependent factors.

Dr Cornilissen does not say if the eight patients they studied with a normal PIVKA-II concentration received certain drugs (such as antibiotics). However, we agree with his conclusion: vitamin K deficiency is rare in patients with cystic fibrosis supplemented with vitamin K.


In a partly similar study Bareford and Hayling10 sent each consultant a monthly statement of use of the laboratory by his firm, compared with that of other clinicians. This practice, with three other interventions, they concluded, resulted in a consistent reduction in inappropriate" (my emphasis) requests for laboratory investigations .

In my opinion, both groups are falling into the trap of making unjustified value judgements based on evidence for only one half of the equation: less tests = better/no worse treatment.

Modifications in clinicians' laboratory testing behaviour patterns can only be regarded as desirable if the "judicious" or "appropriate" behaviour can be demonstrated to improve patient care, or at least to result in no worse care. Similarly, requests can only be regarded as "inappropriate" if it is shown that the test is not needed, or that the results do not influence the clinical care of the patient. Unfortunately, it is almost impossible to measure the quality of patient care in the short term. Misdiaisons, or inappropriate test results from laboratory investigations, which have been done, could only be detected by worsened mortality or morbidity figures obtained over a period of years. Neither Gama et al nor the other group of authors cited above provide any such data to show that clinicians were not giving their patients worse care than before as a result of curtailing their laboratory requests. In fact, Gama et al's statement that as a result of their initiative "fewer outpatients were investigated, and when investigated had fewer tests performed on them" would suggest, prima facie, that these patients were receiving worse medical treatment than before.

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Dr Gama et al comment:

There is ample evidence that many laboratory investigations may be unnecessary for adequate patient care10 and that the recent increased laboratory use has not been associated with an improvement in patient outcome.10 In our study,10 unlike Blecher, we made no unfounded assumption about the quality of patient care. Although we were unable to assess clinical outcome: we agree with Blecher that this, in practice, would be almost impossible to do. We believe it unlikely that the reduction in laboratory use through more thoughtful and discretionary ("judicious") testing adversely affected patient management. The fact that fewer outpatients were investigated suggests the use of venepunctures (considered unnecessary by the attending physician) and this, contrary to Blecher's assertion, represents an improvement in quality of patient care.

Motivation for improving laboratory use should not be limited to better quality of patient care but should also include more efficient use of laboratory personnel and resources.10,11 We believe that this involves tackling not only laboratory overuse12 but also underuse13 and misuse. Gama R, Pickford R, Jones SR, Mauley B, Peters M. Proceedings of the ACB national meeting, 1990:63.

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4. Dr Lefrère et al comment:

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Breast biopsy specimen fixation

Further to the correspondence by Drs Start, Cross, and Smith regarding the procedure of fixing breast biopsy specimens, we add our findings to this debate.

In our view the handling of this kind of specimen poses no dilemma: for best slicing and minimisation of distortion for assessment of resection margins and extent of lesion, the specimen should be fixed before slicing. To overcome this problem we suggest that the specimen should be injected with 10% neutral buffered formalin on receipt then left to fix for 24 hours before slicing.

We use a 10 ml syringe with a 21 gauge needle. The amount of formalin injected depends on the size of the specimen. The injection can be performed by technical staff, which means the specimen need not be sent dry and the pathologist does not have to be on hand when the specimen is received: this may often be the case in a district general hospital.

This technique offers adequate fixation of tissues deep within the specimen while allowing fixation of the outside of which "hardens" the specimen, giving optimal slicing.

There are two possible hazards that need to be borne in mind when using this technique. The first is the danger of needlestick injuries from the secondaries the splashback of formalin which can occur if too much pressure is applied, particularly when injecting firm areas of tissue. Appropriately, appropriate protective clothing should be worn and great care taken when performing this procedure.

We have found a definite improvement using this method in the quality of morphology in subsequent sections compared with those from specimens which were allowed to fix overnight before slicing and were not injected.

We propose that this method helps reduce the inevitable variation in fixation that occurs with these specimens, and thereby reduces the associated variation in mitotic counts which may affect grading. It also improves assessment of resection margins and extent of lesions.

We accept that our findings are subjective and anecdotal, but feel that there is sufficient benefit to merit extending the use of this procedure from localisation biopsy specimens and wide local excision specimens to mastectomy specimens.

**Beckman's reference to the text:**


**AgNOR technique in relation to colorectal neoplasia**

We read with interest the recent paper by Beer et al. because we have also applied this technique to intestinal tissue. This paper is one of a selection that has been published on this topic in recent years in which authors express varied enthusiasm for the method.1-3

We examined 91 surgical resection specimens of large bowel comprising normal mucosa (n = 10); tubular (n = 18), villous (n = 6) and tubulo-villous (n = 16) adenomas; and moderately differentiated adenocarcinomas (n = 22). The batch of malignant tumours comprised five Dukes' A, six B, and 11 C adenomas as described by Smith and Crocker, except that the staining time was one hour; 100 cells were counted.

The results are shown in the table. An unpaired t test was applied to the data and a highly significant difference (p = 0.001) was found between normal mucosa and both the adenomatous polyps and the adenocarcinomas. No statistical difference existed between normal and metaphasic, or between benign

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean (SD)</th>
<th>AgNOR count</th>
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<tbody>
<tr>
<td>Normal mucosa</td>
<td>2.37 (0.28)</td>
<td></td>
</tr>
<tr>
<td>Metaplastic poly</td>
<td>2.71 (0.44)</td>
<td></td>
</tr>
<tr>
<td>Tubular adenoma</td>
<td>3.67 (0.64)</td>
<td></td>
</tr>
<tr>
<td>Villous adenoma</td>
<td>4.12 (0.43)</td>
<td></td>
</tr>
<tr>
<td>Tubulo-villous adenoma</td>
<td>4.62 (0.41)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>4.34 (0.86)</td>
<td></td>
</tr>
</tbody>
</table>

**Summary of results**


**Penetration of 10% neutral buffered formalin into an unshielded 5 cm diameter lump after a single 1 ml injection of fixative.**

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**Beckman's reference to the text:**