PIVKA-II concentrations in patients with cystic fibrosis

Montalembert et al report that PIVKA-II was detected in 33% of patients with cystic fibrosis, while vitamin K, plasma concentrations were normal. It is astonishing that daily doses of 5-10 mg vitamin K₃, 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. Determination of PIVKA-II by monoclonal antibody was found to be the most specific and sensitive method. We did not detect PIVKA-II in any of the eight patients with cystic fibrosis who were supplemented with vitamin K₃ (4–30 mg/day). In only one of the 16 unsupplemented patients with cystic fibrosis was PIVKA-II found (0.16 AU/ml). This patient took antibiotics, had a low vitamin K concentration, of 0.06 µg/l and a Thrombostet of 56%.

The authors do not mention vitamin K₃. Except for vitamin K₃, vitamin K must be accounted for when assessing vitamin K status. Antibiotics may disturb vitamin K₃ production by intestinal flora and hence reduce the amount of total vitamin K available for the carboxylation of PIVKA-II to functional factor II. A correlation between subnormal coagulation tests and antibiotics in cystic fibrosis was reported by Komp and Selden. As there was no information on concentrations of vitamin K₃, it is impossible to establish normal values for vitamin K₃, 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.

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Dr Lefrère et al comment:

Our PIVKA-II assay, based on the activity of staphylocoagulase, is widely used in many laboratories. The results obtained with this procedure with those of laboratories measuring PIVKA-II by monoclonal antibody, in particular in patients with hepato-cellular 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 Cornelissen et al do not raise the possibility of increased PIVKA-II in contexts other than vitamin K deficiency, such as hepato-cellular carcinoma, 1 2 hepato-blastoma, 3 e.g. oral anticagulants and cephalosporins. Indeed, vitamin K deficiency is not the only mechanism to generate PIVKA-II. In hepato-cellular carcinoma increased PIVKA-II concentration is probably due to an acquired enzymatic anomaly which disturbs the γ-carboxylation of all vitamin K dependent factors. 4 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 Cornelissen 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.


Dr Lefrère et al comment:

In their recent paper, Gama et al report that feedback of laboratory data to clinicians "modified" their request behaviour for clinical chemistry and haematology tests (reduced the numbers of tests requested). The authors clearly imply that this modification was a good thing. Their opening sentence refers to "... strategies for improving (my emphasis) laboratory use", and in the discussion they state that their results support the view that "the physicians had become more judicious (my emphasis) in their laboratory use".

In a partly similar study Bareford and Hayling 5 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 substantially greater reduction in inappropriate use. We believe that this involves tackling not only laboratory overuse but also underuse and misuse. Gama R, Pickford R, Jones SR, McCauley B, Peters M. Proceedings of the ACB national meeting, 1990:63.

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 or "judicious" if the modified behaviour can be demonstrated to improve patient care, or at least to result in no worse care. Similarly, requests can only be claimed to be "inappropriate" if it is shown that the tests 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 care 5 and that the recent increased laboratory use has not been associated with an improvement in patient outcome. 6 In our study, 7 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 test. If 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 suggest a decrease in venepunctures (considered unnecessary by the attendant physician) and this, contrary to Blecher's assertion, represents an improvement in the 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 and cost effective use of laboratory resources. 10 11 We believe that this involves tackling not only laboratory overuse but also underuse and misuse. Gama R, Pickford R, Jones SR, McCauley B, Peters M. Proceedings of the ACB national meeting, 1990:63.
Correspondence


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.

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. This is 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 metastatic, or between benign and malignant conditions. AGNOR numbers varied enormously in all but the normal and metastatic states, this being most pronounced in malignancy (figure). No correlation was obtained between the AGNOR number and the Duke's stages, although we acknowledged that relatively few of each stage were examined.

In terms of diagnostic usefulness, our results for colorectal tissue agree with those of Beer et al. and Yu et al. for stromal tumours of the stomach and small intestine. This contrasts with the findings of Yang et al. who discriminated colonic tubular and villous adenomas from adenocarcinomas. Surprisingly, Griffiths et al. could find no link between AGNOR number and neoplasia in large bowel tissue. Unlike us, Other et al. established a correlation between AGNOR number and Dukes' staging.

Clearly, AGNOR number is a reflection of increased cell proliferation and may be used to distinguish normal tissue from neoplastic. However, as an accurate discriminator of malignancy, this technique is inadequate when applied to intestinal tissues. We feel that it offers little more than the haematoxylin and eosin preparation in the area of large bowel diagnostic pathology.

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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 a 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 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 needledistinct injury; the second concerns the splashback of formalin which can occur if too much pressure is applied, particularly when injecting firm areas of tissue. Accordingly, 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.

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Modifying the request behaviour of clinicians.

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