CORRESPONDENCE

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 determinations of 5-10 mg vitamin K, 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 eight patients with cystic fibrosis who were supplemented with vitamin K, (4-30 mg/day). In only one out of 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 Thrombostest of 59%.

The authors do not mention a vitamin K, deficiency. Except for vitamin K, vitamin K, must be accounted for when assessing vitamin K status. Antibiotics may disturb vitamin K, 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 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 it 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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In a partly similar study Bareford and Hayling 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 considerable 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 or “judicious” if it is shown that inappropriate 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 laboratories were not giving their patients worse care than before as a result of curtailing their laboratory requests. In fact, Gama et al’s statement as that 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 care7 8 and that the recent increased laboratory use has not been associated with an improvement in patient outcome. In our study, 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 that the reductions in venepunctures (considered unnecessary by the attending 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 use of laboratory manpower and clinical 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.

De Lefrere et al comment: Our PIVKA-II assay, based on the activity of staphylocoagulate, 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 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 Cornelli et al do not raise the possibility of increased PIVKA-II in contexts other than vitamin K deficiency, such as hepatozell carcinoma, hepatoblastoma, staphylocoagulate, effect of oral anticoagulants and cephalosporins. 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.6 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 Cornelli 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.

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Griffiths AF, Butler CW, Roberts P, Dixon MF, Quirke P. Silver stained structures (AgNORs), their dependence on tissue fixation and absence of prognostic relevance in rectal adenocarcinomas. Histopathology 1990;18:121-7.


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 depended 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 needlestick injuries to the second concern 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.
Modifying the request behaviour of clinicians.

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