A panel of histochemical stains (periodic acid-Schiff technique (PAS)), Grimelius silver stain, oil red O in sections of unprocessed tissue, Alcian blue (AB) pH 2-5, and high iron diamine (HID) reactions, as well as immunohistochemical reactions (monoclonal mouse anti-human carcinoembryonic antigen clone A5B7 DAKO = CEA), tissue polypeptide antigen = TPA, rabbit anti-TPA: B1AB), were done. Immunohistochemical analysis on formalin prefixed paraffin wax embedded tissues showed no cross reactivity of CEA A5B7 to polymorphonuclear neutrophils or erythrocytes. The antibody reacted with colorectal adenocarcinomas (more intense in necrotic debris). PAS was negative, except for small cytoplasmic globules present in occasional tumour cells.

Oil red O, Alcian blue pH 2-5, HID, and Grimelius stains were non-reactive. Immunohistochemical studies showed strong positivity for CEA and TPA. TPA was strongly positive in all tumour cells, particularly in cytoplasm surrounding some of the vacuoles.

A sample from the tumour was prepared for transmission electron microscopy (TEM). The occurrence of multiple, apparently empty vacuoles was confirmed at the TEM level.

A panel of histochemical and immunohistochemical reactions (see above) was applied to sections from three cases of clear cell adenocarcinoma of the kidney. A PAS positive reaction within the vacuoles was recorded in about 50% of the tumour cells; CEA was positive only in the Golgi area in a few cells in some areas, whereas the vacuoles remained unstained. The cell membrane as well as the cytoplasm (but not the vacuoles) were stained in a few tumour cells (<1%) in sections challenged with TPA.

**Necropsy microscopical examination**

Material taken from tumours in the liver, lungs, and omentum at necropsy showed identical structures to those found in the surgical specimen. The kidneys, prostate, and thyroid were normal.

**Discussion**

This case is the sixth clear cell adenocarcinoma of the colon reported. Jewell et al\(^2\) described two cases of clear cell adenoma as well as two cases of clear cell adenocarcinoma of the colon. These investigators concluded that the adenoma–carcinoma sequence, valid for other histological types of colorectal tumours, may also be valid for the clear cell adenocarcinoma of the large intestine.

The strong positivity for TPA present in our case indicates that tumour cells contain a marker that has been found in other adenocarcinomas of the digestive tract.\(^5\)

At histology the colonic tumour was similar with another clear cell adenocarcinoma: clear cell adenocarcinoma of the kidney. The three kidney adenocarcinomas tested here showed a positive reaction for mucopolysaccarides (PAS) and lipids (oil red O), whereas our case of clear cell adenocarcinoma of the colon showed occasional small globules with a PAS positive cytoplasmic substance.

This appears to be the first reported case of clear cell adenocarcinoma of the colon with follow up. The patient had massive metastatic growth at necropsy examination. While no conclusion can be drawn from one case report, it would seem that clear cell adenocarcinoma may be at least as aggressive as other large bowel tumour phenotypes.

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**Introduction of computer assisted control of oral anticoagulation in general practice**

M J Galloway, J J Foggin, S Dixon

**Abstract**

The number of patients referred to hospital clinics for monitoring of oral anticoagulation continues to rise rapidly. Introduction of computer programs for the control of oral anticoagulation improves the quality of anticoagulant control in hospital clinics. This approach has now been extended to include patients managed in general practice. Results confirm that the quality of anticoagulation can also be improved in these patients. A standard ap-
Computer assisted control of oral anticoagulation in general practice

proach to anticoagulation for hospital and community based patients has also fa-
cilitated the transfer of patients on war-
farin from the hospital anticoagulant
clinics to the community with no de-
terioration in the quality of anticoagulant
control. As a result, the workload in the
hospital anticoagulant clinic has fallen for
the first time.

Keywords: Anticoagulants, drug therapy, general prac-
tice.

Previous studies have shown that the in-
roduction of a computer program for de-
termining the dose of oral anticoagulant can lead to
an improvement in the quality of anticoagulant
control in hospital anticoagulant clinics. With
the increasing indications for anticoagulation the
number of referrals to hospital anticoagulant clin-
ics continues to increase, particularly for patients
with atrial fibrillation. As a result of this in-
creasing hospital workload there is pressure to
refer patients back to their general practitioner
for monitoring of their anticoagulation. For this
to be satisfactorily undertaken, it is essential that
the quality of anticoagulant control should not
deteriorate. We have therefore used a previously
reported computer program to determine the
dose of oral anticoagulant for patients managed
in general practice.

Methods
The anticoagulant clinic at Bishop Auckland
Hospitals NHS Trust is held on a weekly basis.
Since 1990, all patients have had their warfarin
dosage controlled using a computer program
for determining the dose of oral anticoagulant.
The clinic is run by a staff pharmacist and
nurse acting under the direction of a consultant
haematologist. The same method for moni-
toring oral anticoagulation was therefore ex-
tended to include patients who did not attend
the hospital anticoagulant clinic.

Ten general practices who use our laboratory
were approached to see if they would agree to
the laboratory taking over the management of
their patients on oral anticoagulants. These
practices were the most distant from the
laboratory. All patients on warfarin were re-
gistered on the anticoagulant clinic computer
and the reasons for anticoagulation were re-
corded. As part of the computer program, the
target international normalised ratio (INR)
range according to the British Society for
Haematology guidelines was allocated. All
general practitioners had previously been cir-
culated with these guidelines.

All general practitioners and practice nurses
in these practices were visited prior to the
start of the study. General practitioners were
asked to send blood samples to the laboratory
on the same day each week. This ensured
that sufficient samples were analysed at the
same time to produce adequate data for
analysis. Each patient sample was ac-
compounded by their anticoagulant book. Once
the INR had been calculated, the dose gen-
erated by the computer was entered into each
patient’s anticoagulant book. These books
were returned to the practice the next morn-
ing. All samples were analysed on the day of
venepuncture. All high INR values were either
telephoned or faxed to each general practice.
During this study, all new patients in these
practices who were started on warfarin were
monitored by this system and were not
seen at the hospital anticoagulant clinic. The
quality of anticoagulant control in these
patients was then compared with those
patients who attended the hospital anticoag-
ulant clinic. The significance of any im-
provement in anticoagulant control was
determined by comparing the mean INR of
each patient group at the beginning and the
end of the study. The workload of the hospital
anticoagulant clinic was also monitored.

Results
Between September 1993 and January 1995,
210 general practice patients were enrolled into
this programme. The INR values for the first
100 patients enrolled are shown in the figure.
Overall, 46% of patients had INR results within
the therapeutic range, this included 55% of
patients whose target INR was 2-0-3-0 and
13% of patients whose target INR was 3-0-4-5
were in the therapeutic range. INR results have
shown a consistent improvement since com-
puter adjusted control of the warfarin dose has
been instituted. The percentage of patients now
in range for these two groups has increased to
72% and 57%, respectively. This improvement
in anticoagulant control was only statistically
significant for those patients whose target INR
range was 3-0-4-5 (table).

As a result of monitoring anticoagulant con-
tral in the community, the hospital anti-
coagulant clinic workload has decreased for
the first time. The total number of patients seen
in the anticoagulant clinic has been increasing
at the rate of 16% per year in the last five years.
Despite a further 6% increase in the number
of new patients referred in the last 12 months,
the total number of patients seen in the hospital
anticoagulant clinic fell by 2% from 3475 to
3405.

Discussion
In this study 46% of patients had INR values
within the therapeutic range prior to the in-
roduction of computer adjusted dosage for
anticoagulation. This is lower than one other
study of anticoagulation in general practice
where 52% of patients were reported as being
within the therapeutic range. This difference
between the two studies appears to be due to
better control of patients whose target INR
was in the range 3-0-4-5. The reasons for this
difference are not clear but may have been
because of a lack of awareness by local general
practitioners of the British Society for Haem-
atology guidelines. However, these guidelines
had been circulated prior to the start of this
study.
INR results for the first 100 patients enrolled into the study:

<table>
<thead>
<tr>
<th>INR value</th>
<th>Hospital patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target INR 3–4–5</td>
<td>3.67 (0.85)</td>
<td>3.57 (1.02)</td>
</tr>
<tr>
<td>Before</td>
<td>2.68 (0.56)</td>
<td>2.37 (0.70)</td>
</tr>
<tr>
<td>After</td>
<td>3.57 (0.85)</td>
<td>3.37 (0.70)</td>
</tr>
</tbody>
</table>

Our study has shown that the introduction of a computer controlled dosage scheme for general practice patients taking warfarin can lead to an improvement in the quality of anticoagulation. This improvement is similar to that observed following the introduction of a computer assisted dosage scheme into a hospital anticoagulant clinic. INR results for those patients monitored in the community are now equivalent to those monitored in the hospital anticoagulant clinic. The implication is that most patients can now have their warfarin treatment monitored satisfactorily in the community without the need for repeated attendance at the hospital anticoagulant clinic. The introduction of this system has allowed non-medical staff to take over the day to day management of patients on warfarin.

We used the existing laboratory transport system to return anticoagulant books to each general practice. One improvement to our service may be to post the anticoagulant book directly to the patient. In view of the number of patients now being monitored, this approach would require additional clerical staff.

In the future it may also be possible to decentralise anticoagulant control further with the introduction of near-patient testing. A number of small coagulometers are now available and are currently undergoing evaluation. Before this approach is introduced, the performance of these coagulometers in general practice must be equivalent to those used in the laboratory, where quality control and quality assurance are closely monitored.

In view of the increasing number of patients referred for anticoagulation, the move towards community based care could have major financial implications. We have not included an economic evaluation in our study. One other study of community based anticoagulation described potential savings of between £8 and £38 per patient visit. This study did not report the use of a computer program to control oral anticoagulant therapy of their patients.

Success in developing anticoagulant control in general practice relies on the co-operation of local general practitioners, practice nurses and patients. Each practice was visited to explain how the programme would operate. This ensured that the transfer of patients to a practice based approach was achieved smoothly. Most patients seem to be happy with the arrangements. We have only had an occasional patient who wished to return to the anticoagulant clinic. This was usually because the patient preferred to have venepuncture performed in the hospital.

We now plan to extend this service to all local general practitioners. We then hope to use the anticoagulant clinic only for initial stabilisation of warfarin dose, patient education and monitoring those patients whose anticoagulation is difficult to control. This approach is likely not only to improve patient care but also to reduce costs.

We are grateful to all general practitioners and their staff in South West Durham who participated in this study. We thank Miss Susan Nicholson for secretarial assistance.