The dangers of giving aspirin or antibiotics to patients on anticoagulant therapy are widely recognised. Aspirin and other salicylates which themselves produce a mild hypoprothrombinaemia are also gastric irritants. Gastrointestinal bleeding may follow the use of these drugs. The possible causes of such bleeding were reviewed by Watson and Pierson (1961). Antibiotic therapy can affect anticoagulant control by interfering with the source of Vitamin K from the intestinal flora and thus indirectly affecting prothrombin production in the liver.

In addition to these there is a growing list of other drugs which potentiate anticoagulant therapy. Attention has recently been drawn to the reduced anticoagulant requirements of certain patients treated with Atromid, a preparation used to reduce serum triglyceride and cholesterol levels (Oliver, Roberts, Hayes, Partridge, Suzman and Beroshn, 1963). A similar effect on anticoagulant therapy was noted by Winters and Soloff (1962) in a patient in whom hypercholesterolaemia was treated with D-thyroxine.

Other drugs reported to potentiate anticoagulant therapy were reviewed by Hellemans (1962) and include dinitrophenol, chlorpromazine, p-amino salicylic acid, testosterone, alcohol and probenecid. Quinine hydrochloride, chloroquine and hydroxychloroquine have also been reported as having an anticoagulant action (Mandel, 1962) and could therefore be expected to exert a synergistic effect on anticoagulant therapy.

Kindermann (1961) reported two cases of spontaneous bleeding after combined therapy with phenindione and phenylbutazone (butazolidin) in the management of superficial thrombophlebitis; and earlier Humble (1953) had reported anomalies in blood clotting in patients on butazolidin. The purpose of this communication is to report a patient on anticoagulant therapy who showed marked prolongation of the prothrombin time and spontaneous bleeding some two weeks after beginning a course of the related compound oxyphenylbutazone (Tanderil).

Case Report

The patient, a printer, with known rheumatic heart disease and a history of angina for nine years, was aged 50 years when, in May 1960, he was admitted to hospital with a posterior myocardial infarct. He was discharged from hospital to continue on long term anticoagulant therapy with phenindione.

A year later in May 1961 he developed multiple small spontaneous bruises and a small subconjunctival haemorrhage, during the course of an upper respiratory tract infection with a productive cough. The Quick one-stage prothrombin time was 3.2 times that of the control plasma (therapeutic range 2.0-2.5). Further slight spontaneous bruising occurred in May
1962. The Thrombotest result at this time was 7.4%, the accepted therapeutic range being 10-15% (Miller, Farrer-Brown and Pether, 1964). No cause was found for this escape from control; the dose of phenindione was slightly reduced and no further bruising occurred.

In August 1962 the patient developed diarrhoea, with 5-6 loose but normal coloured motions each day. Stool culture was negative and the diarrhoea was attributed to phenindione therapy, of which it is a well recognised complication. Accordingly, the drug was discontinued and treatment with warfarin sodium substituted, and within a short time the diarrhoea ceased.

After this the patient continued on anticoagulant therapy without further trouble until the end of April 1964, when he presented with a moderate haemorrhagic effusion into the right olecranon bursa and extensive bruising of the forearm extending from above the elbow to the wrist. The elbow and superior radial-ulnar joints showed a full range of movements and there was no evidence of haemarthrosis. There was no history of trauma, and the patient was otherwise well. The Thrombotest result was now less than 3% of normal, the patient having been reasonably well controlled (see accompanying figure) on a constant dose of warfarin sodium, mean daily dose 9.75 mg., throughout the preceding twelve months. On further questioning it was found that a three week course of oxyphenylbutazone, 100 mg. three times daily, had been prescribed elsewhere for treatment of some "rheumatic" pains of which the patient had complained. The patient had been taking this drug for eighteen days prior to the appearance of the spontaneous bruising. In addition to the oxyphenylbutazone and warfarin sodium, he was taking digitalis and quinidine, both of which had been exhibited since 1960, and also prochlorperazine (Stemetil) prescribed for control of attacks of vertigo since November 1963.

Investigations. Hb. 88% (12.8 g./100 ml.), WBC 5,500/cu.mm., platelets 190,000/cu.mm.. Liver function tests normal—bilirubin less than 0.4 mg./100 ml., thymol turbidity 2, zinc sulphate 6, alkaline phosphatase 7.4 units/100 ml., total protein 6.7 g./100 ml., paper electrophoresis normal, SGOT 20 S.F. units/ml., SGPT 9 units/ml.

Both oxyphenylbutazone and warfarin were discontinued, and the right arm treated by simple support in a sling. After 48 hours, the Thrombotest was still less than 5% of normal. The effusion into the olecranon bursa was aspirated. After five days off anticoagulants the Thrombotest result was 33% of normal and warfarin sodium was recommenced cautiously. The bruising slowly subsided and the arm returned to normal.

Discussion

It is clearly impossible to say with certainty that the escape of this patient from control was attributable to potentiation of anticoagulant therapy by oxyphenylbutazone. However, its occurrence shortly after the exhibition of this drug, the patient having been stable for many months is highly suggestive. None of the other drugs which the patient was taking has been reported to produce this effect. The administration of digitalis to patients in failure will, in fact, often increase the dose of anticoagulant required, presumably by reducing hepatic congestion and so improving liver function. There has been no report of any interaction between Stemetil and anticoagulants in man or in experiments carried out on animals, though there have been reports that another phenothiazine derivative, chlorpromazine, may increase coagulation time in both animals and man. However, these studies are not conclusive and Hrdina and Kovalcik (1964) found that chlorpromazine did not significantly affect the action of the anticoagulants ethylbis-coumacetate and phenindione. It would be unwise in any case, to attempt to predict an effect of a particular phenothiazine derivative on blood clotting on the basis of experimental findings with another.

On the other hand, phenylbutazone, to which Tanderil is closely related and of which it is a metabolite, is known to disturb the blood clotting mechanism, and to produce haemorrhagic complications. Humble (1953) reported on 44 patients on phenylbutazone of whom about one third showed prolongation of the one stage prothrombin time which was sometimes alarming. As a result of studies on these patients he suggested that the clotting defect was due to a deficiency of prothrombin itself and supported this statement by showing that while plasma from these patients could restore to normal the prothrombin time of plasmas deficient in factors V and VII, it failed to do so when added to the plasma of patients with liver disease who are known to have a deficiency of prothrombin.

This known action of the closely related compound, together with the time relationship between the exhibition of oxyphenylbutazone and the onset of escape from control and bleeding lead us to conclude that, in this case, the oxyphenylbutazone potentiated anticoagulant therapy, presumably by a mechanism similar to that produced by phenylbutazone; it must be admitted, however, that Strobel (1963) found no alteration in one stage prothrombin time, fibrinogen or platelet count after oxyphenylbutazone...
It seemed to us important to draw attention to the possible haemorrhagic hazards of combined therapy with anticoagulants and phenylbutazone or its derivatives. There are, of course, other side effects of phenylbutazone which make such combined therapy a matter for caution. Mauer (1955) reviewed the literature on the toxicity of phenylbutazone and summarised reports from 26 papers covering a total of 3934 patients. In this series he found 415 patients with upper gastrointestinal symptoms with 23 cases of gastrointestinal bleeding and 40 cases of peptic ulcer. Other toxic manifestations included 32 cases of thrombocytopenia, as well as diarrhoea, toxic hepatitis, rash, blood dyscrasias, water retention and cardiac decompensation. Oxyphenylbutazone is generally accepted as having the same adverse reactions as the parent compound, though possibly giving rise to fewer gastrointestinal disturbances. (Council on Drugs 1963).

An annotation in the British Medical Journal (1962) estimated that some 100,000 persons were probably receiving phenylbutazone each week. The widespread use of this drug and related compounds makes it important that the hazards of such therapy should be widely known. It would seem wise for reasons discussed above to avoid using these drugs in the treatment of patients who are already receiving anticoagulants. If, however, in a particular patient, this combination of drugs seems necessary, extremely careful control of anticoagulant therapy is advisable.

Summary

Attention is drawn to the growing list of drugs reported to potentiate anticoagulant therapy.

A case is reported of a patient, well controlled for many months on a constant dose of warfarin sodium, in whom a dramatic fall in prothrombin time followed the administration of Tanderil.

Great caution is advised in undertaking combined therapy with this drug, or its parent compound phenylbutazone, and anticoagulants.

We wish to thank Professor Sir Charles Dodds for his interest and Dr. J. D. N. Nabarro for his permission to publish clinical details of this patient. Also we acknowledge with thanks the great help given by Pharmaceutical Specialities (May and Baker) Ltd. who searched the literature and their personal reports for information on the effect of Stemetil on blood coagulation. We are also grateful to Evans Medical Ltd. and the Geigy Pharmaceutical Co. Ltd. for information supplied; and to those who helped us with problems in translation.

REFERENCES