known to be oculotoxic, and the eyes cleared up within 48 hours after stopping rifampicin. He was put on isoniazid, ethambutol, and streptomycin without any untoward reactions and he became AFB-negative. He was later discharged on oral isoniazid and ethambutol.

Signs of toxicity in a patient taking various combinations of antituberculosis drugs

Drug regimen	Ocular toxicity	Liver function tests	Other toxicity
None	–	Normal	–
Isoniazid, ethambutol, and rifampicin	+	Normal	–
Isoniazid, PAS, and streptomycin	–	Normal	Vomiting, nausea
Isoniazid (one week)	–	Normal	–
Isoniazid and rifampicin	+	Normal	–
Isoniazid, ethambutol, and streptomycin	–	Normal	–

Comment

Clearly the exudative conjunctivitis in this case might have been due to rifampicin—perhaps a kind of hypersensitivity or idiosyncratic reaction.

[1] *Extra Pharmacopoeia: Martindale*, ed N W Blacow and A Wade, 26th edn, p 1416. London, Pharmaceutical Press, 1972.

Bevendean Hospital, Brighton BN2 4DS
F E CAYLEY, MD, FRCP, consultant physician-superintendent
SISIR K MAJUMDAR, MB, BSC, senior house officer

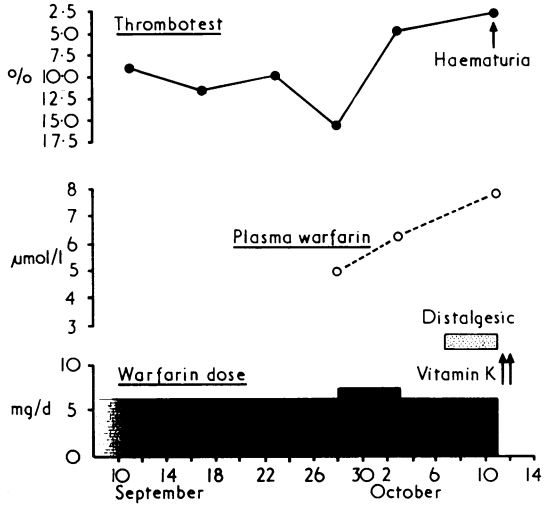
Warfarin and Distalgesic interaction

Many patients receiving long-term anticoagulant treatment with warfarin require an analgesic from time to time. Current practice suggests that they should not be given acetylsalicylic acid because of an increasing risk of haemorrhage. It is common clinical practice, therefore, to recommend either paracetamol or Distalgesic for pain relief in these patients. We report two patients on warfarin who had definite haematuria when given Distalgesic (dextropropoxyphene hydrochloride and parautamol.)

Case reports

Case 1—A 55-year-old man presented in July 1972 with a deep vein thrombosis of his left leg, which was confirmed by venography. He was well controlled initially on 6 mg of warfarin daily but on 28 September his thrombotest was 16% and his dose of warfarin was increased to 7 mg/day (the plasma warfarin concentration at this stage was 4·9 μmol/l (1·5 μg/ml)). On 3 October the dose of warfarin was reduced back to 6 mg per day because the thrombotest was only 5% (the plasma warfarin concentration was now 5·9 μmol/l (1·8 μg/ml)). On 11 October he presented with marked haematuria and his thrombotest was less than 5%. He had had an episode of back pain on 6 October for which he had taken Distalgesic, two tablets three times daily. The plasma warfarin concentration on admission was 7·8 μmol/l (2·4 μg/ml), having risen from 5·9 μmol/l (1·8 μg/ml) in spite of the reduction in the dose of warfarin. He was given vitamin K and his haematuria disappeared over the next three days.

Case 2—A 75-year-old woman was first seen in November 1974, when she presented with dyspnoea and pleuritic chest pain and a diagnosis of pulmonary embolism was made. She was treated with heparin and then maintained on warfarin and, on a steady dose of 7 mg/day, the prothrombin time varied between 30 and 40 seconds (optimal anticoagulant control 28-36 seconds). On 6 January 1975, after six weeks' treatment with warfarin she was prescribed Distalgesic for a pain in her leg. She took six tablets between 1200 and 1800 hours and presented in casualty at 2300 hours with gross haematuria. Her prothrombin time was 130 seconds and, after being given 10 mg vitamin K, the haematuria resolved over the succeeding four days. No measurements of plasma warfarin concentration were made.



Thrombotest percentages, plasma warfarin concentrations, and warfarin daily dosages in case 1. Plasma warfarin concentrations were measured by the method of Lewis *et al.*[5]
Conversion: SI to traditional units—Warfarin: 1 μmol/l ≈ 0·31 μg/ml.

FURTHER STUDIES

To examine the possible mechanism whereby Distalgesic might potentiate the effect of warfarin, studies were done with dextropropoxyphene in both man and rats. Paracetamol has been shown not to interfere significantly with the hypoprothrombinaemic effect of warfarin, in the usual clinical doses of up to 3·0 g per day.[1 2] Dextropropoxyphene in concentrations of 3·0 μmol/l (1·0 μg/ml), 14·7 μmol/l (5·0 μg/ml), and 29·5 μmol/l (10·0 μg/ml) did not displace warfarin (16·3 μmol/l (5·0 μg/ml)) from protein-binding sites in human plasma in studies using an ultrafiltration technique.[3]

Groups of rats were treated with dextropropoxyphene in a dose of 20 mg/kg, and the sleeping times and plasma half-lives of ^{14}C-pentobarbitone were recorded.[4] The mean pentobarbitone sleeping time in a group of 10 rats treated with dextropropoxyphene was 156·4 ± 9·1 (SEM) minutes while that of the control rats given saline was 106·8 ± 5·9 minutes ($P<0.005$). The half-life of ^{14}C-pentobarbitone (30 mg/kg) was 202·0 ± 27·8 (± 95% confidence limits) minutes in the animals treated with dextropropoxyphene, compared with 101·0 ± 9·5 minutes in the control animals.

Discussion

In both patients Distalgesic apparently potentiated the hypoprothrombinaemic effect of warfarin, with resultant haematuria. Our studies suggest that dextropropoxyphene does not displace warfarin from plasma-protein-binding sites. Animal studies suggest that dextropropoxyphene inhibits the metabolism of pentobarbitone, as judged by pentobarbitone sleeping time and half-lives. Dextropropoxyphene is metabolised by the same liver microsomal enzymes that hydroxylate warfarin and might compete for metabolism. This inhibition of warfarin metabolism is supported by the measurement of plasma warfarin concentrations, which rose from 5·9 μmol/l (1·8 μg/ml) to 7·8 μmol/l (2·4 μg/ml) in the first patient when given distalgesic in spite of a reduction in the dose of warfarin.

[1] Antilitz, A M, *et al*, *Current Therapeutic Research*, 1968, **10**, 501.
[2] Udall, J A, *Clinical Medicine*, 1970, **77(8)**, 20.
[3] Toribara, T Y, *Journal of Clinical Investigation*, 1957, **36**, 738.
[4] Breckenridge, A, *et al*, *Clinical Science*, 1971, **40**, 351.
[5] Lewis, R J, *et al*, *Biochemical Medicine*, 1970, **4**, 376.

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12
M ORME, MD, MRCP, assistant lecturer (now senior lecturer, Department of Pharmacy and Therapeutics, University of Liverpool)
A BRECKENRIDGE, MD, FRCP, senior lecturer (now professor of clinical pharmacology in the University of Liverpool)

Whittington Hospital, London N19
P COOK, MB, MRCP, medical registrar (now at University College Hospital, London)