**Phenformin as a fibrinolytic drug**

**G. R. FEARNLEY**

**M.D., F.R.C.P.**

*Physician, Gloucestershire Royal Hospital*

During the past 20 years fibrinolysis, once an apparently rare and pathological phenomenon, has begun to emerge as the physiological antithesis of coagulation, a system whose function seems to be the removal of fibrin. Basically the system consists of plasminogen, an inactive enzyme precursor present in blood and other body fluids which can be converted to plasmin, an active proteolytic enzyme, by activators present in the blood, body fluids and the tissues. Anti-plasmin is present in blood and neutralizes any plasmin liberated, so that in normal circumstances free plasmin is absent from circulating blood and the fibrinolytic system is in effect inert.

Since plasmin digests fibrinogen as well as fibrin, antiplasmin is a necessary safeguard against destruction of fibrinogen in fluid blood; but when fibrin is formed activator is adsorbed to it and converts the plasminogen incorporated with it to plasmin which in turn is adsorbed to fibrin.
and hence protected from inactivation by anti-
plasmin. Thus protected, the plasmin is free to
digest deposited fibrin.

This forms the basis of a concept of natural
fibrinolysis shown in Fig. 1, whereby the fibrino-
lytic system functions as a fibrin-clearing and
hence antithrombotic mechanism without impairing
haemostasis (Fearnley, 1953, 1961). Normal
blood contains an activator of plasminogen
(Fearnley & Tweed, 1953; Flute, 1960) which
varies between individuals, and appears to be
deficient in 60% of patients with peripheral ar-
teriosclerosis (Fearnley & Chakrabarti, 1964), and
in 45% of male survivors of myocardial infarc-
tions under the age of 60, as compared with
10% of age-matched controls (Chakrabarti et
al., 1966).

Natural fibrinolytic activity is conveniently
measured by the dilute-blood-clot lysis-time
(Fearnley, Balmforth & Fearnley, 1957) in which
the time required for lysis of a 1 in 10 dilution
of freshly obtained blood clotted with thrombin
is measured at 37°C. Fibrinolytic activity is in-
versely proportional to the lysis-time. Normal
lysis-times by this method range from 1½ to 7 hr.

Some years ago it occurred to me that it might
be possible to enhance the fibrinolytic activity of
blood pharmacologically with the object of de-
veloping a new approach to the prophylaxis of
vascular occlusion in patients with ischaemic dis-
ease.

**Background**

At that time the only pharmacological sub-
stance, as distinct from the thrombolytic agent
streptokinase, known to increase blood fibrino-
lytic activity was adrenaline, as was first shown
by Biggs, Macfarlane & Pilling (1947), using a
dilute-plasma-clot test-system. When Biggs et al.
(1947) published their results spontaneous fibrin-
olytic activity had not been shown to be a nor-
amal property of blood, and the appearance of
fibrinolytic activity in diluted plasma was be-
lieved to be a reaction of the body to stress. Fol-
lowing the observation that fibrinolytic activity
induced by adrenaline is labile in fluid blood
and plasma, but is stabilized by fibrin formation
(Fearnley, Revill & Tweed, 1952), fibrinolytic ac-
tivity was found to be a property of normal
blood, as already mentioned. The problem there-
fore seemed to be one of enhancing something
which is normally present, but there was no clue
as to what kind of drug might do this or for
that matter whether such a drug existed. Early
pilot trials of sympathomimetic drugs given by
mouth, ephedrine, dextroamphetamine and iso-
prenaline, gave disappointing results; and exper-
iments with other commonly used therapeutic
substances, including single doses of prednisone,
were equally unproductive. In 1959 my colleagues
and I decided to test insulin for any possible
effect on fibrinolysis. The subcutaneous injection
of insulin in diabetics was found to result in a
biphasic fibrinolytic response, consisting of an
initial reduction followed by an increase of blood
fibrinolytic activity, as measured by the dilute-
blood-clot lysis-time (Fearnley, Vincent & Chak-
rabarti, 1959). The increase of fibrinolytic ac-
tivity coincided with low blood-glucose levels
and was postulated to be due to release of adrenaline.
This suggested that sulphonurea compounds
might increase blood fibrinolytic activity, and tol-
butamidine and chlorpropamide were found to do
so in arteriosclerotic patients studied in the fast-
ing, resting state (Fearnley, Chakrabarti & Vin-
cent, 1960). Since increased fibrinolytic activity
was not accompanied by reduction of blood
-glucose levels in our patients, hypoglycaemia was
evidently not the cause of the fibrinolytic effect
of these compounds. Although subsequent ex-
perience showed that many people become re-
sistant to the fibrinolytic effect of the sulphony-
ureas (Fearnley & Chakrabarti, 1964), these were
the first substances discovered to enhance fibrin-
olytic activity for several weeks when given
by mouth.

It seemed possible that hormones might in-
fluence the fibrinolytic system, and testosterone
given intramuscularly in large dosage daily or on
alternate days was found to produce a sustained
increase of fibrinolytic activity (Fearnley & Chak-
rabarti, 1962; Winther, 1967). As a result of this
finding, the anabolic steroids, methenolone and
ethyloestrenol, given by mouth were investigated
for fibrinolytic effects. Both increased fibrino-
lytic activity, but as with the sulphonyleureas
resistance developed in many patients within a
few weeks (Fearnley & Chakrabarti, 1964). In
the meantime ACTH and corticosteroids were
shown to increase fibrinolytic activity both in
patients with inflammatory and with non-inflammatory conditions, the latter indicating the effect of corticosteroids on fibrinolysis to be primary and specific, rather than a reflection of improvement of inflammation (Chakrabarti, Fearnley & Hocking, 1964).

The diguanides

The fibrinolytic effect of the sulphonylureas, though disappointingly temporary, suggested that other drugs which influence carbohydrate metabolism might also enhance fibrinolytic activity. Phenformin in tablet form, 100–150 mg daily, was found to increase fibrinolytic activity but caused too high an incidence of gastric intolerance; when timed-release capsules became available these in a dosage of 50 mg twice daily were well tolerated by most patients and produced an increase of fibrinolytic activity in the majority, which was sustained when the drug was evaluated for a period of 3 months (Fearnley & Chakrabarti, 1964). The allied substance metformin in a dosage of 500 mg thrice daily was found to have a comparable fibrinolytic effect in patients with coronary artery disease (Chakrabarti, Hocking & Fearnley, 1965). Subsequently resistance was found to develop to the fibrinolytic effects of both phenformin and metformin after 3–4 months' treatment (Hocking et al., 1967).

Combined fibrinolytic drugs

The problem of resistance which seemed to develop sooner or later to the fibrinolytic effect of drugs given by mouth prompted us to investigate combined therapy.

In a trial lasting 21 months the effects on the dilute-blood-clot lysis-time, the euglobulin lysis-time, plasma fibrinogen and serum cholesterol levels of metformin 1-0 g daily plus ethyloestrenol 8 mg daily were studied in fifteen patients with occlusive vascular disease and of phenformin capsules 100 mg daily plus ethyloestrenol 8 mg daily in eighteen patients. Both combinations given over a period of 12 months produced a sustained increase of fibrinolytic activity in 80% and 89% of the patients respectively. The diguanides were then withdrawn for 3 months, the patients continuing to take ethyloestrenol alone, which failed to maintain the full fibrinolytic effect of combined treatment. When metformin and phenformin were restituted for the last 6 months of the trial, the full fibrinolytic effect was restored. Both combinations of drugs reduced plasma fibrinogen levels; serum cholesterol was reduced by phenformin but not by metformin (Fearnley, Chakrabarti & Hocking, 1967). The results obtained with phenformin plus ethyloestrenol are shown in Fig. 2.

![Fig. 2. Effect of phenformin plus ethyloestrenol on mean serum cholesterol, plasma fibrinogen, dilute blood clot lysis-time (BLT) and euglobulin lysis-time (ELT) compared with metformin, phenformin, and ethyloestrenol alone in eighteen patients with occlusive vascular disease. (From Fearnley, G.R., Chakrabarti, R. & Hocking, E.D., 1967, Lancet, ii, 1008.)](http://pmj.bmj.com/)

Phenformin combined with ethyloestrenol was also found to reduce platelet stickiness by about 50% in fifteen of twenty patients with occlusive vascular disease (Chakrabarti & Fearnley, 1967) as shown in Fig. 3. Metformin with ethyloestrenol does not have this effect (unpublished data).

Applications

Since phenformin with ethyloestrenol favourably influences four factors believed to be of importance in the genesis of vascular occlusions, i.e. fibrinolytic activity, plasma fibrinogen, serum cholesterol, and platelet stickiness, this combination of drugs would seem to be suitable for trial in the prophylaxis of arterial occlusions in patients with ischaemic disease, for example, survivors of myocardial infarction. Serious toxicity has not so far been encountered, and gastric intolerance to phenformin of sufficient severity...
to cause cessation of treatment occurs in less than 5% of patients. The full effects of the drugs, and this applies especially to reduction of platelet stickiness, are not apparent, however, in many patients until they have been given for up to 3 months. It follows that should phenformin plus ethyloestrenol exercise a protective effect in atherosclerotic patients over-all benefit could not be expected during the first 2–3 months of treatment. We are at present conducting a pilot trial of this combination of drugs in survivors of a first attack of myocardial infarction below the age of 60.

Fig. 3. Mean reduction of platelet stickiness by phenformin plus ethyloestrenol in ten patients. (From Chakrabarti, R. & Fearnley, G.R., 1967, Lancet, ii, 1012.)

An entirely different aspect of pharmacological fibrinolysis is its relevance to the treatment of chronic inflammatory conditions in which deposition and persistence of fibrin may be a causative factor in continuing inflammation. The finding that corticosteroids increase fibrinolytic activity suggested that this might be a component of their therapeutic action, and led to the trial of fibrinolytic drugs in rheumatoid arthritis. Phenformin plus ethyloestrenol were given to twenty patients with rheumatoid arthritis, twelve of whom improved clinically together with reduction of plasma fibrinogen level and blood sedimentation rate. When treatment was interrupted in five patients they relapsed and regained improvement when phenformin plus ethyloestrenol were given again (Fearnley & Chakrabarti, 1966).

Pharmacological fibrinolysis is a new therapeutic concept, which now that the resistance which develops to fibrinolytic drugs given orally has been overcome by combined treatment seems suitable for trial in ischaemic and chronic inflammatory conditions.

References


