TREATMENT — THE RESISTANT CASE

Is there a place for proteinase inhibition? A review of the literature

G. D. LISTER

University Department of Surgery, Glasgow Royal Infirmary

Summary

The evidence demonstrating excessive proteinase activity in states of shock is reviewed. The capacity of extrinsic inhibitors to control such activity is indicated and the literature showing the value of inhibitors in treating shock is summarized. Three principles to be observed in the use of exogenous inhibitors are proposed.

PROTEINASE is the generic term for proteolytic enzymes. Proteolysis occurs in the processes of digestion and during autolysis. In more controlled form, it is the basis of certain homeostatic processes in which the proteinases are activators and pro-activators, the control being exercised by inhibitor systems.

In disease or following trauma, the activity of these systems increases as an essential part of the attempt to restore the physiological state. This is desirable, but on occasion activity increases to an extent which overwhelms the intrinsic inhibitor mechanisms. This is highly undesirable as it results, separately or in combination, in acute haemostatic defects, intravascular coagulation, redistribution of the blood volume and, as a result, in profound disturbances of haemodynamics which contribute to inadequate tissue perfusion. In such circumstances of excessive, harmful proteinase activity, the temporary redress of the disturbed intrinsic balance by the administration of exogenous proteinase inhibitors would be a desirable therapeutic step.

Many such extrinsic inhibitors, ranging from aspirin to certain amino acids, are available and they have been reviewed by Back (1966). Their very varied activity has been analysed, with particular reference to fibrinolysis, by McNicol & Douglas (1964) who showed that only six are of practical value:

- ϵ -Amino caproic acid (EACA).
- Tranexamic acid.
- 1-(Aminomethyl)cyclohexane-4-carboxylic acid (AMCHA).
- p*-Aminomethyl benzoic acid (PAMBA).
- Parotid proteinase inhibitor (Trasylol).
- Pancreatic proteinase inhibitor (Iniprol).

Of these, only EACA and parotid proteinase inhibitor appear sufficiently frequently in the literature to warrant review.

In order to present the evidence for the involvement of proteinase systems in the state of shock and to examine the value of extrinsic inhibition in controlling those systems and in treating shock, the three hinted at above, namely coagulation, fibrinolysis and vasoactivity, will be considered. Hardaway (1965) and his group of workers (Rutherford, West & Hardaway, 1966) have shown that intravascular coagulation is a feature of haemorrhagic, endotoxin and traumatic shock; Nordström, Olsson & Blomback (1965) have demonstrated increased circulating thromboplastin after surgery and shown experimentally that equivalent levels lead to massive intravascular thrombus formation; such thrombi have been observed by electron microscopy in endotoxin shock by McKay, Margaretten & Csavossy (1967). The anticoagulant properties of parotid proteinase inhibitor in clear contrast to EACA have been shown by Amris (1966) and by Dubber *et al.* (1968), while Nordström *et al.* (1965) in the work referred to above, showed that it prevented intravascular coagulation in their experimental preparations.

Uninhibited vasoactivity with resultant widespread vasodilatation and pooling of blood mainly in the splanchnic bed has been shown to be a factor in endotoxin shock by several groups (Gilbert, 1960; Weil, Sudnamis & Shubin, 1962; Brockman, Thomas & Vasko, 1967). Such abnormal vasodilatation in other forms of refractory shock has been postulated, and, in an attempt to assess this, estimation of vasoactive polypeptide activity using the method of Diniz and his co-workers (1961) has been undertaken. The literature is summarized in Table 1, all the papers having shown evidence of increased vasoactivity, while the three groups who assessed proteinase inhibition found it to be of value. Attar *et al.* (1967) have found a correlation clinically between mortality and depletion of vasoactive precursors. Corrado, Reis & Carvalho (1966) have shown experimentally that irreversible shock is associated with a fall of bradykininogen to less than 50% of control levels.

TABLE 1. Documented evidence: increased vasoactive polypeptide links in shock

Aetiology	Reference	Clinical	Experimental	Proteinase inhibition
Haemorrhage	Webster & Clark (1959)		*	
	Meyer (1966)		*	
	Attar <i>et al.</i> (1967)	*		
Endotoxin	Webster & Clark (1959)		*	
	Kobold, Lucas & Thal (1963)	*		
	Meyer & Werle (1964)		*	+
	Greeff (1966)		*	
	Meyer (1966)		*	
	Attar <i>et al.</i> (1967)	*		
Anaphylaxis	Rothschild & Castania (1968)		*	
	Beraldo (1950)		*	
	Greeff (1966)		*	
	Back (1969)		*	
Miscellaneous	Thal, Kobold & Hollenberg (1963)	*	*	+
	Kobold & Thal (1963)	*	*	
	Ryan, Moffat & Thompson (1965)		*	+
	Greeff (1966)	*	*	
	Attar <i>et al.</i> (1967)	*		

In its most overt and dramatic form, excessive fibrinolytic activity as a complication of surgical procedures and obstetric accidents is widely recognized and the literature has been reviewed by Sharp (1964) who also lays down strict criteria for the use of EACA in combating such states. That fibrinolysis occurs to a sub-clinical degree in disease and following trauma or immunological challenge has been demonstrated by several groups and the evidence is summarized by Sherry, Fletcher & Alkjaevsig (1959) and by Eisen (1964).

In such lesser degrees of uncontrolled fibrinolysis, particularly in view of the frequently coincidental presence of intravascular coagulation, EACA, with its propensity to induce coagulation, can have no place. It is, therefore, pertinent that the ability of Trasylol to inhibit fibrinolysis has been shown, experimentally and clinically, by several groups (Steichele & Herschlein, 1961; Beck, Schmutzler & Duckert, 1963; Tice *et al.*, 1964; Amris, 1966), while the kinetics of the inhibition have recently been analysed by Dubber and her co-workers (1968).

Indeed, in attempting to reverse such combined sub-clinical defects of haemostasis and vasoactivity as would contribute to the inadequacy of tissue perfusion, parotid proteinase inhibitor offers several advantages over EACA:

- (1) EACA, while inhibiting plasminogen activation, is less powerful an inhibitor of plasmin activity (Tice *et al.*, 1963; McNicol & Douglas, 1964);
- (2) EACA does not inhibit kininogen activation (Eisen, 1964);
- (3) EACA carries a risk of intravascular coagulation (Naeye, 1962; Sharp, 1964; Crosby, 1967); and

- (4) Parotid proteinase inhibitor has approximately 1000 times the molar potency of EACA (Dubber *et al.*, 1968).

The evidence presented that excessive proteinase activity may occur in states of shock does not show whether that excessive activity is a contributory factor to the severity of shock or merely one of its consequences. It does not follow, therefore, that to show that such excessive activity can be controlled by exogenous inhibitors means that their administration will assist in treating shock. It is necessary to seek evidence on the direct value of proteinase inhibition in improving shocked cases.

Proteinase inhibitor has been shown experimentally to reduce mortality and prolong survival in shock due to endotoxin (Czeizel, Gorgenyi & Kertal, 1966), trauma, anaphylaxis (Back, 1969) and peritonitis (Meyer, 1965). Clinically, Tice *et al.* (1963, 1964) have used Trasylol to advantage after extracorporeal circulation, while Morl & Heller (1969) found that its administration reduced by half the mortality due to peritonitis in a controlled series. In the remaining literature, pancreatitis is the model against which proteinase inhibition is measured. As arrest of trypsin autodigestion must play an important role in any benefit which extrinsic inhibition confers, such work is not relevant to this assessment.

Conclusion

Thus, direct evidence defining the value of proteinase inhibition in the treatment of shock is scanty. It would be, therefore, premature to recommend its use. On the same grounds of lack of evidence it cannot be condemned but must be referred for trial.

In approaching such trials, three rules must be

clearly enunciated and closely observed:

(1) The dosage must be adequate. That recommended has risen steadily (Forell, 1960) in a somewhat empirical fashion, which has suggested inefficacy and inspired scepticism, but the titration studies of Goldberg & Roy (1965) have demonstrated that doses in excess of 100,000 units/hr are essential.

(2) Inhibitor must be administered by continuous infusion, its half-life in plasma being only 8 min.

(3) The dynamic nature of the state which is being treated allied with the need to inhibit, rather than combat or reverse, dictates that only immediate administration can offer hope of success (McHardy *et al.*, 1963; McCutcheon & Race, 1963; Smith *et al.*, 1963; Meyer & Werle, 1964; Back, 1969).

References

- AMRIS, C.J. (1966) Inhibition of fibrinolytic and thrombolytic activity by Trasylol. *Scand. J. Haemat.* **3**, 19.
- ATTAR, S.M.A., TINGEY, H.B., McLAUGHLIN, J.S. & COWLEY, R.A. (1967) Bradykinin in human shock. *Surg. Forum*, **18**, 46.
- BACK, N. (1966) Fibrinolysin system and vasoactive kinins. *Fed. Proc.* **25**, 77.
- BACK, N. (1969) Shock and proteinase inhibitors. *Proc. Symp. Trasylol Therapy, London*, 1968.
- BECK, E., SCHMUTZLER, R. & DUCKERT, F. (1963) Inhibition of fibrinolysis and fibrinogenolysis in man; comparison of ϵ -aminocaproic acid and kallikrein inhibitor. *Thrombos. Diathes. hemorrh.* (Stuttgart), **10**, 106.
- BERALDO, W. (1950) Formation of bradykinin in anaphylactic and peptone shock. *Amer. J. Physiol.* **163**, 283.
- BROCKMAN, S.K., THOMAS, C.S. & VASKO, J.S. (1967) The effect of *Escherichia coli* endotoxin on the circulation. *Surg. Gynec. Obst.* **125**, 763.
- CORRADO, A.P., REIS, M.L. & CARVALHO, I.F. (1966) Bradykininogen and bradykinin in the cardiovascular shock produced by proteolytic enzymes. *Biochem. Pharmacol.* **15**, 959.
- CROSBY, W.H. (1967) *Hemorrhagic Complications in Surgery*. Saunders, Philadelphia.
- CZEIZEL, E., GORGENYI, F. & KERTAL, P. (1966) Pharmacological control of endotoxin effects. *Acta physiol. hung.* **30**, 364.
- DINIZ, C., CARVALHO, I., RYAN, J. & ROCHAE, S. (1961) A micromethod for the determination of bradykininogen in blood plasma. *Nature (Lond.)*, **192**, 1194.
- DUBBER, A.H.C., McNICOL, G.P., UTTLEY, D. & DOUGLAS, A.S. (1968) *In vitro* and *in vivo* studies with Trasylol, an anticoagulant and a fibrinolytic inhibitor. *Brit. J. Haemat.* **14**, 31.
- EISEN, V. (1964) Fibrinolysis and vasoactive polypeptides. *Brit. med. Bull.* **20**, 205.
- FORELL, M.M. (1960) Treatment of acute pancreatitis by intravenous administration of trypsin inactivator. *Gastroenterology*, **38**, 964.
- GILBERT, R.P. (1960) Mechanism of the hemodynamic effects of endotoxin. *Physiol. Rev.* **40**, 245.
- GOLDBERG, D.M. & ROY, A.D. (1965) Trasylol and acute pancreatitis. *Brit. med. J.* **2**, 943.
- GREEFF, K. (1966) The kininogen content of the plasma in experimentally produced shock. *New Aspects of Trasylol Therapy*. Schattauer-Verlag, Stuttgart.
- HARDAWAY, R.M. (1965) Coagulation in shock in various species including man. *Acta chir. scand.* **130**, 157.
- KOBOLD, E.E., LUCAS, R. & THAL, A.P. (1963) Chemical mediators in clinical septic shock. *Surg. Forum*, **14**, 16.
- KOBOLD, E.E. & THAL, A.P. (1963) Quantitation and identification of vasoactive substances liberated during various types of experimental and clinical intestinal ischemia. *Surg. Gynec. Obstet.* **117**, 315.
- MEYER, A. (1965) Current view of the biochemistry, clinical aspects and therapy of peritonitis. *Langenbecks Arch. klin. Chir.* **313**, 182.
- MEYER, A. (1966) The action of Trasylol in states of shock. *New Aspects of Trasylol Therapy*. Schattauer-Verlag, Stuttgart.
- MEYER, A. & WERLE, E. (1964) The influence of the kallikrein inhibitor Trasylol on endotoxin shock. *Diseases of the Exocrine Pancreas*, p. 299. Schattauer-Verlag, Stuttgart.
- MORL, F.K. & HELLER, W. (1969) Shock and proteinase inhibitors. *Proc. Symp. Trasylol Therapy, London*, 1968.
- MCCUTCHEON, A.D. & RACE, D. (1963) Experimental pancreatitis: use of a new antiproteolytic substance, Trasylol. *Ann. Surg.* **158**, 233.
- McHARDY, G., CRAIGHEAD, C.C., BALART, L., CRADIC, H. & LAGRANGE, C. (1963) Pancreatitis: intrapancreatic proteolytic trypsin activity. Evaluation of trypsin inhibitor. *J. Amer. med. Ass.* **183**, 527.
- MCKAY, D.G., MARGARETTEN, W. & CSAVOSSY, I. (1967) An electron microscope study of endotoxin shock in Rhesus monkeys. *Surg. Gynec. Obstet.* **125**, 825.
- McNICOL, G.P. & DOUGLAS, A.S. (1964) Epsilon-aminocaproic acid and other inhibitors of fibrinolysis. *Brit. med. Bull.* **20**, 233.
- MAEYE, R.L. (1962) Thrombotic state after a hemorrhagic diathesis, a possible complication of therapy with epsilon-aminocaproic acid. *Blood*, **19**, 694.
- NORDSTRÖM, S., OLSSON, P. & BLOMBACK, M. (1965) Thromboplastin-induced hypercoagulability and its prevention. *Nature (Lond.)*, **206**, 632.
- ROTHSCHILD, A.M. & CASTANIA, A. (1968) Endotoxin shock—plasma kininogen depletion. *J. Pharm. Pharmacol.* **20**, 77.
- RUTHERFORD, R.B., WEST, L. & HARDAWAY, R.M. (1966) Coagulation changes during hemorrhagic shock. *Ann. Surg.* **164**, 203.
- RYAN, J.W., MOFFAT, J.G. & THOMPSON, A.G. (1965) Role of bradykinin system in acute hemorrhagic pancreatitis. *Arch. Surg. (Chicago)*, **91**, 14.
- SHARP, A.A. (1964) Pathological fibrinolysis. *Brit. med. Bull.* **20**, 240.
- SHERRY, S., FLETCHER, A.P. & ALKJAEVSIK, N. (1959) Fibrinolysis and fibrinolytic activity in man. *Physiol. Rev.* **39**, 343.
- SMITH, R.B., ORAHOOD, R.C., WANGENSTEEN, S.L., BERAKHA, G.J. & ZAMELIS, A. (1963) The effect of trypsin-inhibitor in experimentally induced pancreatitis in the dog. *Surgery*, **54**, 922.
- STEICHELE, D.F. & HERSCHLEIN, H.J. (1961) Zur anti-fibrinolytischen Wirkung des Trypsin-Kallikrein-Inaktivators. *Med. Welt*, **42**, 2170.
- THAL, A.P., KOBOLD, E.E. & HOLLENBERG, M.J. (1963) The release of vasoactive substances in acute pancreatitis. *Amer. J. Surg.* **105**, 708.
- TICE, D.A., WORTH, M.H., CLAUSS, R.H. & REED, G.H. (1963) Hemorrhage due to fibrinolysis occurring with open-heart operations. *J. thorac. cardiovasc. Surg.* **46**, 673.
- TICE, D.A., WORTH, M.H., CLAUSS, R.H. & REED, G.H. (1964) The inhibition by Trasylol of fibrinolytic activity associated with cardiovascular operations. *Surg. Gynec. Obstet.* **119**, 71.
- WEBSTER, M.E. & CLARK, W.R. (1959) Significance of the callicrein-callidinogen-callidin system in shock. *Amer. J. Physiol.* **197**, 406.
- WEIL, M.H., SUDNAMIS, R.B. & SHUBIN, H. (1962) Treatment of endotoxin shock. *California Med.* **96**, 86.