Thrombolytic experience with brinase

Clinical experience with brinase

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The rationale for clinical investigation of brinase may be summarized as follows:

Local Administration

Rapid thrombolysis with low doses by direct proteolytic effect; no or insignificant lowering of systemic inhibitors thus no effect on coagulation factors; thrombolytic effect not plasminogen dependent.

Systemic Administration

Slower thrombolysis by partial depletion of systemic inhibitors; effect on inhibitors and the coagulation system dose-related; thrombolytic effect not plasminogen dependent.

The thrombolytic effect of brinase after local administration was investigated in occluded cannulae and indwelling catheters permitting direct observation of the effect. In 105 cases instillation of 2 to 5 ml (1 mg/ml) of brinase resulted in lysis of the occlusion within three to 10 minutes. Inhibitor levels were not affected and no side effects were observed. Local administration of streptokinase (28 000 units) for 60 to 100 minutes was without effect on the occlusions (13 cases). Subsequent instillation of brinase freed the catheters within two to five minutes (Hartzell and Holmdahl, 1971).

In multicentre trials in Canada and in Europe brinase was investigated in 558 completely occluded arterial or venous external haemodialysis shunts. Two to 5 ml of brinase solution (1 mg/ml in the European study and 0.5 mg/ml in the Canadian trial) was instilled into the occluded shunt part. At intervals of five to 15 minutes the solution was replaced until the shunt was patent or until 50 ml solution had been used. The immediate results are summarized in the Table.

In the majority of cases an effect was obtained within 20-40 minutes. Plasma inhibitors in the systemic circulation were not affected. Possible explanations for the observed differences in efficacy in the two studies were discussed.

Transient local pain subsequent to lysis of the occlusion was the most frequently observed side effect, which, however, did not interfere with treatment. Moreover, upon shunt leakage skin reactions were reported and in six cases symptoms indicating sensitization after repeated administration.

Reliable and rapid thrombolytic effects could thus be obtained in these studies without obvious signs of drug toxicity. In most cases significant prolongation of shunt life could be achieved by repeated brinase treatment. The procedure has now been accepted for routine use in clotting complications of external haemodialysis shunts.

Intraarterial instillation of brinase close to the

Brinase Solution	Recanalization				Failure	Total	
		Complete	Partial				
European study	No.	203	37		28	268	
1 mg/ml (1000 C2-units)	%		76	14	10		100
Canadian study	No.	178	26		86	290	
0.5 mg/ml (500 C2-units)	%		61	9	30		100
Total	No.	381	63		114	558	
	%		68	11	21		100

Table Declotting of occluded external haemodialysis shunts by local instillation of brinase.¹

¹Immediate treatment results: complete recanalization—blood flow restored to preclotting rate and volume; partial recanalization blood—flow at less than preclotting rate and volume dialysis possible; failure—surgical relocation of shunt required.

occlusion was studied in three patients suffering from acute thrombosis of the superficial femoral or the popliteal artery. Brinase was given in a volume of 50 to 100 ml (1 mg/ml) with repeated arteriographic control. Total or partial recanalization within one hour was achieved in these cases. At the same time local reactions (oedema and local epidermolysis) were observed (Lund, Hellström, and Frisch, 1968). The mechanism responsible for these side effects was studied in dogs. The results indicated an interaction between protein breakdown products formed during thrombolysis with brinase and the repeated injection of x-ray contrast medium as the probable explanation for the observed local reactions in man (Frisch, Lund, Moller, Hedin, and Magnusson, 1971). Clinical investigations will be resumed within a short time.

To estimate the potential value of brinase in the treatment of pulmonary embolism a series of dog experiments was carried out. Rapid dissolution (within four hours) could be achieved by instillation of high doses of brinase into the pulmonary artery. Transient affection of the coagulation system without haemorrhage was recorded (Amundsen, Eie, and Roe, 1971).

Composite List of References

- Alkjaersig, N., Fletcher, A. P., and Sherry, S. (1959). *J. clin. Invest.*, **38**, 1086.
- Ambrus, C. M., and Markus, G. (1960). *Amer. J. Physiol.*, **199**, 491.
- Amundsen, E., Eie, H., and Roe, J. (1971). To be published.
- Andrews, P. (1967). *Lab. Pract.*, **16**, 851.
- Arocha-Piñango, C. L. (1967). *Acta cien. Venez.*, **18**, 136.
- Arocha-Piñango, C. L., and Layrisse, M. (1969). *Lancet*, **1**, 810.
- Astrup, T. (1968). *Ann. N.Y. Acad. Sci.*, **146**, 601.
- Astrup, T., and Müllertz, S. (1952). *Arch. Biochem.*, **40**, 346.
- Astrup, T., and Nissen, U. (1964). *Nature (Lond.)*, **203**, 255.
- Bartlett, R. C. (1963). *Clin. Chem.*, **9**, 317.
- Beller, F. K., Mitchell, P. S., and Gorstein, F. (1967). *Thrombos. Diathes. haemorrh. (Stuttg.)*, **17**, 427.
- Bennett, N. B. (1967). *Thrombos. Diathes. haemorrh. (Stuttg.)*, **17**, 12.
- Bennett, N. B. (1970). *Thrombos. Diathes. haemorrh. (Stuttg.)*, **23**, 553.
- Bennett, N. B., Ogston, C. M., McAndrew, G. M., and Ogston, D. (1966). *J. clin. Path.*, **19**, 241.
- Bennett, N. B., Ogston, C. M., and Ogston, D. (1968). *J. Physiol. (Lond.)*, **198**, 479.
- Bergkvist, R., and Svård, P. O. (1964). *Acta physiol. scand.*, **60**, 363.
- Berry, E. W., Sharp, A. A., and Allington, M. J. (1970). In *Proceedings of the XIIIth International Congress of Haematology, Munich, August, 1970*.
- Biggs, R., Macfarlane, R. G., and Pilling, J. (1947). *Lancet*, **1**, 402.
- Bonnar, J., Davidson, J. F., Pidgeon, C. F., McNicol, G. P., and Douglas, A. S. (1969). *Brit. med. J.*, **3**, 137.
- Bonnar, J., McNicol, G. P., and Douglas, A. S. (1969a). *Brit. med. J.*, **3**, 387.
- Bonnar, J., McNicol, G. P., and Douglas, A. S. (1969b). *J. Obstet. Gynaec. Brit. Cwlth*, **76**, 799.
- Bonnar, J., McNicol, G. P., and Douglas, A. S. (1970). *Brit. med. J.*, **2**, 200.
- Bonnar, J., Prentice, C. R. M., McNicol, G. P., and Douglas, A. S. (1970). *Brit. med. J.*, **2**, 564.
- Brakman, P., and Astrup, T. (1963). *Scand. J. clin. Lab. Invest.*, **15**, 603.
- Brakman, P., Mohler, E. R., Jr., and Astrup, T. (1966). *Scand. J. Haemat.*, **3**, 389.
- Bygdeman, S. (1967). *Life Sci.*, **6**, 499.
- Cash, J. D. (1966). *Brit. med. J.*, **2**, 502.
- Cash, J. D., and Allan, A. G. E. (1967a). *Brit. J. Haemat.*, **13**, 376.
- Cash, J. D., and Allan, A. G. E. (1967b). *Brit. med. J.*, **1**, 545.
- Cash, J. D., and Woodfield, D. G. (1967). *Nature (Lond.)*, **215**, 628.
- Cash, J. D., and Woodfield, D. G. (1968). *Brit. med. J.*, **2**, 658.
- Chait, A., Summers, D., Krasnow, N., and Wechsler, B. M. (1967). *Amer. J. Roentgenol.*, **100**, 364.
- Coccheri, S., Borgatti, E., Loreti, A., and Gennari, P. (1964). *G. Clin. med.*, **45**, 1434.
- Coccheri, S., Ollendorff, P., and Astrup, T. (1969). *Thrombos. Diathes. haemorrh. (Stuttg.)*, **22**, 35.
- Cunningham, G. M., Boyd, G., Windebank, J., Moran, F., and McNicol, G. P. (1970). To be published.
- Dalal, P. M., Shah, P. M., Allington, M. J., and Sharp, A. A. (1969). Unpublished observations.
- Davis, B. J. (1964). *Ann. N.Y. Acad. Sci.*, **121**, 404.
- Denis, P. S. (1838). *Essai sur l'Application de la Chimie à l'Étude Physiologique du Sang de l'Homme et à l'Étude Physiologico-pathologique Hygiénique et Thérapeutique des Maladies de cette Humeur*. Bechet, Paris.
- Dioguardi, N., Mannucci, P. M., Lotto, A., Rossi, P., Levi, G. F., Lomanto, B., Rota, M., Mattei, G., Proto, C., Fiorelli, G., and Agostoni, A. (1971). *Lancet*, **2**, 891.
- Egeblad, K. (1967). *Scand. J. Clin. Lab. Invest.*, **20**, Suppl. 98.
- Ehringer, H., and Fischer, M. (1968). *Med. Welt.*, **32**, 1726.
- Ekelund, H., Hedner, U., and Nilsson, I. M. (1970). *Acta paediat. Scand.*, **59**, 33.
- European Working Party (1971). *Brit. med. J.*, **3**, 325.
- Fagerhol, M. (1971). In *International Symposium on Proteolysis and Pulmonary Emphysema, City of Hope National Medical Center, Duarte, California, 4-6 January, 1971*.
- Fearnley, G. R. (1965). *Fibrinolysis*. Williams and Wilkins, Baltimore.
- Fearnley, G. R., and Chakrabarti, R. (1968). *Lancet*, **2**, 1004.
- Fearnley, G. R., Chakrabarti, R., and Hocking, E. D. (1967). *Lancet*, **2**, 1008.
- Fletcher, A. P. (1964). In *Blood Coagulation, Hemorrhage and Thrombosis*, edited by L. Tocantins and L. Kazal, pp. 254-260. Grune and Stratton, New York.
- Fletcher, A. P. (1970). In *Cerebrovascular Survey Report for Joint*

- Council Subcommittee on Cerebrovascular Disease, edited by R. G. Siekert, pp. 148-163. National Institute of Neurological Diseases and Stroke and National Heart and Lung Institute, Whiting, Rochester.
- Fletcher, A. P., Alkjaersig, N., O'Brien, J., and Tulevski, V. G. (1970). *Trans. Ass. Amer. Physcs.* 83, 159.
- Fletcher, A. P., Alkjaersig, N., Sherry, S., Genton, E., Hirsh, J., and Bachmann, F. (1965). *J. Lab. clin. Med.*, 65, 713.
- Fogarty, T. J., Cranley, J. J., Krause, R. J., Strasser, E. S., and Hafner, C. D. (1963). *Surg. Gynec. Obstet.*, 116, 241.
- Fred, H. L., Axelrad, M. A., Lewis, J. M., and Alexander, J. K. (1966). *J. Amer. med. Ass.*, 196, 1137.
- Freedman, H. J., and Roschlau, W. H. E. (1970). *Canad. J. Physiol. Pharmacol.*, 48, 69.
- Frisch, P., Lund, F., Møller, G., Hedin, L., and Magnusson, G. (1971). In *Proceedings of the 6th European Conference on Micro-circulation, Aalborg*, 1970, p. 399. Karger, Basel.
- Ganrot, P. O., and Niléhn, J. E. (1968). *Clin. chim. Acta*, 22, 335.
- Gottlob, R., Blümmel, G., Piza, F., Brücke, P., Böhmig, H. J. (1968). *Thrombos. diathes. haemorrh.* (Stuttg.), 19, 516.
- Green, J. R. (1887). *J. Physiol. (Lond.)*, 8, 372.
- Hartzell, L., and Holmdahl, M. T. (1971). To be published.
- Hedin, S. G. (1903). *J. Physiol. (Lond.)*, 30, 195.
- Hedner, U., Nilsson, I. M., and Robertson, B. (1966). *Thrombos. Diathes. haemorrh.* (Stuttg.), 16, 38.
- Hedner, U., Nilsson, I. M., and Jacobsen, C. D. (1970). *Scand. J. clin. Lab. Invest.*, 25, 329.
- Hess, H. (1967). *Arterielle Embolism und Thrombosen. Schattauer, Stuttgart.*
- Hirsh, J., Hale, G. S., McDonald, I. G., McCarthy, R. A., and Pitt, A. (1968). *Brit. med. J.*, 4, 729.
- Hunter, J. (1794). *A Treatise on the Blood, Inflammation and Gun-shot Wounds*, p. 87. Nicoll, London.
- Iatridis, S. G., and Ferguson, J. H. (1963). *J. appl. Physiol.*, 18, 337.
- Isacson, S., and Nilsson, I. M. (1970). *Scand. J. Haemat.*, 7, 404.
- Isacson, S., and Nilsson, I. M. (1972). *Acta chir. scand.*, in press.
- James, K., Taylor, F. B., Jr., and Fudenberg, H. H. (1967). *Biochim. biophys. Acta (Amst.)*, 133, 376.
- Johnson, A. J., Kline, D. L., and Alkjaersig, N. (1969). *Thrombos. Diathes. haemorrh.* (Stuttg.), 21, 259.
- Kakkar, V. V., Flanc, C., Howe, C. T., O'Shea, M., and Flute, P. T. (1969). *Brit. med. J.*, 1, 806.
- Knight, C. S. (1967). *Advanc. Chromat.*, 4, 61.
- Kohn, J. (1967). *Clin. Chim. Acta*, 2, 297.
- Konttinen, Y. P. (1968). *Fibrinolysis*. Oy Star Ab, Tampere, Finland.
- Kwaan, H. C., Coccheri, S., and Astrup, T. (1967). In *Proceedings of the 1st International Symposium on Tissue Factors and Homeostatic Coagulation Fibrinolytic System*, Florence, p. 165.
- Latallo, Z. S., and Teisseyre, E. (1971). *Scand. J. Haemat.*, in press.
- Latallo, Z. S., Węgrzynowicz, Z., Teisseyre, E., and Kopec, K. (1971). *J. Haemat. Scand.*, in press.
- Laurell, C. B. (1965). *Analyt. Biochem.*, 10, 358.
- Laurell, C. B. (1966). *Analyt. Biochem.*, 15, 45.
- Lauritsen, O. S. (1968). *Scand. J. clin. Lab. Invest.*, 22, 314.
- Lund, F., Hellström, L., and Frisch, P. (1968). *Opusc. med. (Stockh.)*, 13, 281, 396.
- Macfarlane, R. G. (1937). *Lancet*, 1, 10.
- Mackay, N., Ferguson, J. C., and McNicol, G. P. (1970). *J. clin. Path.*, 23, 789-796.
- McNicol, G. P., Bain, W. H., Walker, F., Rifkind, B. M., and Douglas, A. S. (1965). *Lancet*, 1, 838.
- McNicol, G. P., and Douglas, A. S. (1965). *Brit. med. J.*, 1, 1149.
- Martin, M., Schoop, W., and Zeitler, E. (1969). *Herz-Kreislauf*, 1, 31.
- Miller, G. A. H., Gibson, R. V., Honey, M., and Sutton, G. C. (1969). *Brit. med. J.*, 1, 812.
- Morawitz, P. (1906). *Beitrag chem. Physiol. Path.*, 8, 1.
- Müllertz, S. (1953). *Acta physiol. Scand.*, 28, 29.
- Nilsson, I. M., Krook, H., Sternby, N. H., Söderberg, E., and Söderström, N. (1961). *Acta med. Scand.*, 169, 323.
- Nilsson, I. M., and Robertson, B. (1968). *Thrombos. Diathes. haemorrh.* (Stuttg.), 20, 297.
- Ogston, D., and McAndrew, G. M. (1964). *Lancet*, 2, 1205.
- Ogston, D., Ogston, C. M., and Fullerton, H. W. (1966). *Thrombos. Diathes. haemorrh.* (Stuttg.), 15, 220.
- Ogston, D., Ogston, C. M., Ratnoff, O. D., and Forbes, C. D. (1969). *J. clin. Invest.*, 48, 1786.
- Pandolfi, M., Isacson, S., and Nilsson, I. M. (1969). *Acta med. Scand.*, 186, 1.
- Pandolfi, M., Nilsson, I. M., Robertson, B., and Isacson, S. (1967). *Lancet*, 2, 127.
- Pandolfi, M., Robertson, B., Isacson, S., and Nilsson, I. M. (1968). *Thrombos. Diathes. haemorrh.* (Stuttg.), 20, 247.
- Paraskevas, M., Nilsson, I. M., and Martinsson, G. (1962). *Scand. J. clin. Lab. Invest.*, 14, 138.
- Parfentjev, I. A., Johnson, M. L., and Clifton, E. E. (1953). *Arch. Biochem.*, 46, 470.
- Poliwoda, H., Alexander, K., Buhl, V., Holsten, D., and Wagner, H. H. (1969). *New Engl. J. Med.*, 280, 689.
- Poulain, M., Renard, M. J., and Josso, F. (1964). *Hémostase*, 4, 307.
- Reid, W. O., Holburn, R. R., DeSipin, M. T., and Tocantins, L. M. (1965). *Amer. J. med. Sci.*, 249, 518.
- Reid, W. O., Hodge, S. M., and Cerutti, E. R. (1967). *Thrombos. Diathes. haemorrh.* (Stuttg.), 18, 179.
- Ritz, N. D. (1965). *N.Y. St. J. Med.*, 65, 2914.
- Roschlau, W. H. E. (1964). *Canad. J. Physiol. Pharmacol.*, 42, 109.
- Roschlau, W. H. E. (1968). *Canad. med. Ass. J.*, 98, 757.
- Roschlau, W. H. E., and Fisher, A. M. (1966). *Angiology*, 17, 670.
- Roschlau, W. H. E., Freedman, H. J., and Miller, S. L. (1969). *Canad. J. Physiol. Pharmacol.*, 47, 61.
- Roschlau, W. H. E., and Tosoni, A. L. (1965). *Canad. J. Physiol. Pharmacol.*, 43, 731.
- Sasahara, A. A., Cannilla, J. E., Belko, J. S., Morse, R. L., and Criss, A. J. (1967). *New Engl. J. Med.*, 277, 1168.
- Sautter, R. D., Fletcher, F. W., Emanuel, D. A., Lawton, B. R., and Olsen, T. G. (1964). *J. Amer. med. Ass.*, 189, 948.
- Scheidegger, J. J. (1955). *Int. Arch. Allergy*, 7, 103.
- Schmidt, E., Poliwoda, H., Buhl, V., Alexander, K., and Schmidt, F. W. (1969). IVth Int. Congress of Clin. Pathology. Montreal.
- Schmutzler, R. (1968). *Angiologica*, 5, 119.
- Schmutzler, R., Fritze, E., Gebauer, D., Gillmann, H., Heckner, F., Korte, P., Van de Loo, J., Pezold, F. A., Poliwoda, H., Praetorius, F., and Zekorn, D. (1971). In *19th Annual Symposium on Blood*, Wayne State University School of Medicine, Detroit, January, 1971.
- Schoop, W., Martin, M., and Zeitler, E. (1968). *Dtsch. med. Wschr.*, 93, 2321.
- Semar, M., Skoza, L., and Johnson, A. J. (1969). *J. clin. Invest.*, 48, 1777.
- Spöttl, F., and Holzknecht, F. (1970). *Thrombos. Diathes. haemorrh.* (Stuttg.), 24, 100.
- Strauss, H. S., Kevy, S. V., and Diamond, L. K. (1965). *New Engl. J. Med.*, 273, 301.
- Svärd, P.-O. (1966). *Scand. J. Haemat.*, 3, 277.
- Svensden, P. J., and Rose, C. (1970). *Science Tools. The (LKB) Instrument Journal*, 17, 13.
- Thompson, C. M., Jr. (1967). *Lab. Pract.*, 16, 968.
- Tow, D. E., Wagner, H. N., Jr., and Holmes, R. A. (1967). *New Engl. J. Med.*, 277, 1161.
- Urokinase Pulmonary Embolism Trial Study Group (1970). *J. Amer. med. Ass.*, 214, 2163.
- Verstraete, M., Amery, A., and Vermeylen, J. (1963). *Brit. med. J.*, 1, 1499.
- Von Kaulla, K. N., and Schultz, R. (1958). *Amer. J. clin. Path.*, 29, 104.
- Weiner, M., Redisch, W., and Weisberg, L. (1959). *Thrombos. Diathes. haemorrh.* (Stuttg.), 3, 358.
- Winckelmann, G., Hiemeyer, V., Weissleder, H., and Schoop, W. (1963). *Dtsch. med. Wschr.*, 88, 2331.
- Woodfield, D. G., Cole, S. K., and Cash, J. D. (1968). *Amer. J. Obstet. Gynec.*, 102, 440.