Correspondence

Chemonucleolysis

To the Editor:

In his recent review of chemonucleolysis, Deutman discusses pros and cons in the use of chymopapain for the treatment of discogenic sciatica (Deutman 1992). This treatment modality for sciatica due to lumbar disc herniation was introduced about 30 years ago (Smith 1964) and its popularity has shown considerable variations over the years. Following initial clinical trials over many years, chymopapain was released for more general use about 10 years ago both in the U.S.A. and in European countries. Following this more general introduction, a number of serious complications were reported in terms of neurological injuries, for example, lumbar subarachnoid hemorrhage and paraplegia (Eguro 1983, Weitz 1984, Agre 1985, Brown 1985, Dyck 1985). These neurological complications may not have been frequent, but they were serious enough to make the popularity pendulum swing back towards a reluctant, negative approach regarding the use of chymopapain in the treatment of disc herniation (Nachemson and Rydevik 1988). Deutman does not discuss why these complications occurred. On the contrary, he states that "Chymopapain in itself is not neurotoxic." However, it has clearly been shown that chymopapain can induce both structural and functional neural injury, acute and long-term, in animal experiments (Rydevik et al. 1976, Zook and Kobrine 1986). This effect seems to be based on the fact that chymopapain causes acute microvascular injury with hemorrhage and edema in the nerve tissue, if the enzyme comes in direct contact with the neural tissue (Brånemark et al. 1969, Rydevik et al. 1976, Olmarker et al. 1990). These findings may well explain hemorrhage and neurologic complications which have been reported following injection of chymopapain in the subarachnoid space, where it may come in direct contact with the microvessels in, for example, the meninges and the nerve roots. Thus, chymopapain has certain neurotoxic properties, and must therefore be handled with due care if used for intradiscal injection. There is a close anatomical relationship between the intervertebral disc and the neural tissue in nerve roots and cauda equina, and therefore even a slightly misplaced injection needle may lead to improper placement of chymopapain with risk for neurological complications.

Deutman also states that "Complications are short-term and limited to the operative and immediate post-operative period". I do not think that this is completely correct; allergic reactions to chymopapain may well be acute and short-term but certain neurological complications, if they occur, are likely to be long-term. However, it should be emphasized that severe neurologic complications are rare, and such complications have become gradually less frequent over the last few years, as compared to the situation 10–15 years ago (Nordby 1989). This may be related to a more controlled and exact intradiscal injection technique being used, carefully avoiding needle penetration of the subarachnoid space and the nerve roots (Tregonning et al. 1991)

When evaluating the clinical results from prospective, double-blind randomized studies, comparing the results of chymopapain to placebo (Javid et al. 1983, Fraser 1984, Gogan and Fraser 1992), one must consider the fact that the so-called placebo injection of an interverterbal disc with, for example, saline may induce negative effects on the disc tissue with disc swelling and elevated intradiscal pressure as a result (Editorial 1986). A more relevant control group vs. chymopapain injection than intradiscal saline injection would be "nothing", i.e., the natural history of sciatica in a matched control group of patients. To my knowledge, such a prospective, controlled randomized study has not been performed.

Surgery for lumbar disc herniation with sciatica seems to give more predictable and better results, with the least risk for a second procedure (Watts et al. 1975, Ejeskär et al. 1983, Crawshaw et al. 1984, van Alphen et al. 1988). However, the key issue in this regard is, of course, the patient selection for the respective treatment modality. Future work, evaluating the role of various predictive factors for the treatment outcome after surgery or chemonucleolysis, including the role of, for example, MRI, may clarify some of these critical issues.

Chemonucleolysis has certain attractive features; it can be done under local anesthesia and there is no surgical incision and thus no post-operative wound. However, data from prospective controlled randomized studies indicate that the clinical results of chymopapain treatment may not match those of surgical

removal of the disc herniation, performed on correct indications and with a proper technique (Watts et al. 1975, Ejeskär et al. 1983, Crawshaw et al. 1984, van Alphen et al. 1988, Tregonning et al. 1991). Any alternative to surgical treatment of disc herniation must be shown to compare favorably to this established and well documented treatment modality. This is a real challenge for future work in this field.

References

Agre K. Serious neurological adverse events associated with administration of chymodiactin (R). In: Chemonucleolysis (Ed. Nordby E J), Slack Inc. 1985.

van Alphen H A M, Braakman R, Berfelo M, Broere G, Bezemer P D, Kostanse P J. Chemonucleolysis or discectomy? Results of a randomized multicentre trial in patients with a herniated intervertebral disc. Acta Neurochir 1988; (suppl 43): 35–8.

Brown M D. Paraplegia following chymopapain injection. A case report (letter). J Bone Joint Surg (Am) 1985; 67 (3): 504.

Brånemark P-I, Ekholm R, Lundskog J. Tissue response to chymopapain in different concentrations. Animal investigations on microvascular effects. Clin Orthop 1969; 67: 52–67.

Crawshaw C, Frazer A M, Merriam W F, Mulholland R C, Webb J K. A comparison of surgery and chemonucleolysis in the treatment of sciatica. A prospective randomized trial. Spine 1984; 9 (2): 195–8.

Deutman R. The case for chemonucleolysis in discogenic sciatica. A review. Acta Orthop Scand 1992; 63 (5): 571–575.

Dyck P. Paraplegia following chemonucleolysis. A case report and discussion of neurotoxicity. Spine 1985; 10 (4): 359–62.

Editorial. Chymopapain and the intervertebral disc (editorial) Lancet 1986; 2 (8511): 843–5.

Eguro H. Transverse myelitis following chemonucleolysis. Report of a case. J Bone Joint Surg (Am) 1983; 65 (9): 1328–30.

Ejeskär A, Nachemson A, Herberts P, Lysell E, Anderson G, Irstam L, Peterson L E. Surgery versus chemonucleolysis for herniated lumbar discs. A prospective study with random assignment. Clin Orthop 1983; 174: 236–42.

Fraser R D. Chymopapain for the treatment of intervertebral disc herniation. The final report of a double-blind study. Spine 1984; 9(8):815–8.

Gogan W J, Fraser R D. Chymopapain: A 10-year, double-blind study. Spine 1992; 17 (4) :388–94.

Javid M J, Nordby E J, Ford L T. Safety and efficacy of chymopapain (chymodiactin) in herniated nucleus pulposus with sciatica. Results of a randomised double-blind study. JAMA 1983; 249: 2489–94.

Nachemson A L, Rydevik B. Chemonucleolysis for sciatica. A critical review. Acta Orthop Scand 1988; 59 (1): 56–62.

Nordby E J. Chemonucleolysis for sciatica. Letter to the Editor. Acta Orthop Scand 1989; 60 (2): 235–8.

Olmarker K, Danielsen N, Nannmark U, Sennerby L, Rydevik B: Microvascular effects of chondoitinase ABC and chymopapain. An in vivo experimental study on hamsters and rabbits. Clin Orthop 1990; 257: 274–9.

Rydevik B, Brånemark P-I, Nordborg C, McLean W G, Sjöstrand J, Fogelberg M: Effects of chymopapain on nerve tissue. An experimental study on the structure and function of peripheral nerve tissue in rabbits after local application of chymopapain. Spine 1976; 1: 137–48.

Smith L. Enzyme dissolution of the nucleus pulposus in humans. JAMA 1964; 187: 137–40.

Tregonning G D, Transfeldt E E, McCulloch J A, MacNab I, Nachemson A. Chymopapain versus conventional surgery for lumbar disc herniation. 10-year results of treatment. J Bone Joint Surg (Br) 1991; 73 (3) 481–6.

Zook B C, Kobrine A I. Effects of collagenase and chymopapain on spinal nerves and intervertebral discs of cynomolgus monkeys. J Neurosurg 1986; 64 (3):474–83.

Watts C, Hutchison G, Stern J, Clark K. Comparison of intervertebral disc disease treatment by chymopapain injection and open surgery. J Neurosurg 1975; 42 (4): 397–400.

Weitz E M. Paraplegia following chymopapain injection. A case report. J Bone Joint Surg (Am) 1984; 66 (7): 1131–5.

Björn Rydevik, M.D.
Department of Orthopaedics
University of Gothenburg
Sahlgren Hospital
S-413 45 Gothenburg, Sweden

To the Editor:

With such a rich history of controversy on the subject of chemonucleolysis, it is not surprising that the debate continues. But in view of scientific facts, critics (Nachemson 1992) lean towards acceptance of its efficacy. Dr. Rydevik raises important issues in his comments. Chymopapain, if used intradiscally, is a safe drug. The dura serves as a barrier if an epidural leakage should occur. I did not discuss intrathecal use of the drug, for there is nowadays ample evidence that erroneous needle technique can be held responsible for (most) observed neurologic complications. As stated: "intrathecal injection of chymopapain can lead to interruption of the microcirculation of nerve tissue." Damage to nerve tissue is secondary (Nordby 1991). However, there is common agreement that toxic manifestations of chymopapain result from proteolysis of the glycosaminoglycan (GAG) structure of capillaries (Stern 1985). Complications of chymopapain, if injected intradiscally, are short-term and limited (Nordby 1986, Gogan and Fraser 1992). Saline injection may have negative short term effects (Editorial 1986), but to my knowledge, as in discography, there have never been long-term effects on the disc tissue. So, results of saline injection are likely to be a reflection of the natural history of intervertebral disc prolapse (Gogan and Fraser 1992).

The number of second procedures after chemonucleolysis is likely to decrease during the learning curve. However, one has to accept the influence of the surgeon on these numbers. Our statistics indicate that a second procedure in the same year for whatever reason, was performed in 3 percent in the past 5 years (550 procedures). I agree with Dr. Rydevik that there remains a real challenge, part of which is to convince surgeons that there is an alternative to surgical treatment without scarring. This was the exact reason for stating my case for chemonucleolysis.

References

Editorial. Chymopapain and the interverebral disc (editorial). Lancet 1986; 2 (8511): 843–5.

Gogan W J, Fraser R D. Chymopapain: A 10-year, double-blind study. Spine 1992; 17 (4): 388–94.

Nachemson A L. Newest knowledge of low back pain: A critical look. Clin Orthop 1992; 279: 8–21.

Nordby E J. Long term results in chemonucleolysis. Editorial comment. Clin Orthop 1986; 206:2–3.

Nordby E. J. Chemonucleolysis. In: The Adult Spine: Principles and Practice, J W Frymoyer, Editor-in-Chief. Raven Press Ltd., New York 1991: 1733–1750.

Stern I J. The biochemistry and toxicology of chymopapain. In: Chemonucleolysis (Eds. Brown, J.E, Smith, L.) Slack Inc, Thorofare1985.

Robert Deutman M.D., Ph.D.
Department of Orthopedics, Martini Hospital
Postbus 30033
NL-9700 RM Groningen
The Netherlands