Taking the bite out of snake venoms.(Feature)

by Kathryn Senior

Anticoagulant and procoagulant substances in snake venoms may have therapeutic uses in the treatment of stroke, blood vessel occlusive diseases, ptosis, and other conditions. Anticlotting agents in venom help to rapidly distribute it in the bloodstream to quickly disable the snake's prey. Researchers have treated stroke patients with ancrod, a drug produced from pit viper venom, and report results superior to tissue plasminogen activator. Fibrolase from copperhead rattlesnake venom causes blood clots to dissolve, and may be useful in patients with peripheral vascular disease. A substance that promotes clotting in rattlesnake venom may be useful as a tissue adhesive.

It is 40 years since it was first realised that the physiologically active components of snake venoms might have therapeutic potential. Some toxins-eg, notexin from the Australian mainland tiger snake (Notechis scutatus)-are being actively investigated for clinical use, but there is also interest in snake-venom proteins that inhibit blood coagulation. For snakes, these proteins are important because they help toxins spread quickly through the body of the prey so that it dies before it can escape. For us, they may provide therapies for acute stroke and thrombosis.

As yet, relatively few snake-venom proteins have been tested clinically. One that has is ancrod, a protease from the venom of the Malayian pit viper (Agkistrodon rhodostoma). Ancrod removes fibrinogen from the circulation without converting it to fibrin, and, although ancrod is thrombin-like, it does not cause platelet aggregation. In February, David Sherman (University of Texas Science Center, San Antonio, TX, USA) and colleagues announced the results of a 500-patient trial of ancrod in people who had had a stroke. 50% of the patients (average age 73 years) were given ancrod within 3 hours of the onset of stroke symptoms. Controls received standard supportive therapy or tissue-type plasminogen activator when it became available. "The initial ancrod dose, which was given double-blinded, was based on bodyweight and serum fibrinogen concentrations. We then monitored fibrinogen values in individual patients and modified the dose of ancrod to keep them within a target range", explains Sherman.

At 90 days, 42[middle dot]2% of patients given ancrod and 34[middle dot]4% of controls had regained 100% independence or returned to their prestroke degree of independence, a "significant difference", claims Sherman. "The performance of ancrod was particularly promising given that the patients had had severe strokes and were about 5 years older than those usually enrolled in stroke trials", he adds. Peter Sandercock (University of Edinburgh, UK) is more cautious: "The benefits of ancrod were only just significant and the confidence intervals were large. The trial was not really big enough to establish a definite positive risk/benefit ratio."

Two other trials of snake-venom therapy for stroke are due to report in 2001. ESTAT, another ancrod trial, has recently increased its sample size to more than 1000 patients, and, in China, a 2400-patient trial of defibrase has just finished recruitment. Defibrase, from A actus and A halysussuriensis, works in a similar way to ancrod. Ming Liu (West China University of Medical Sciences, Chengdu, China) says that about 30% of Chinese doctors use snake-venom products routinely to treat stroke and view them as effective and relatively safe. But, she admits, "there is not enough randomised evidence to support this view yet".

Many snake venoms also contain fibrinolytic agents and Frank Markland (University of Southern California, Los Angeles, USA) predicts that enzymes such as fibrolase from the southern copperhead snake (A contortrix contortrix) could be developed as treatment for occlusive arterial or venous thrombotic disease. Fibrolase degrades fibrin and fibrinogen directly and "in animal studies, produces rapid, specific, and consistent thrombolysis. Since fibrolase works differently to plasminogen activators, it has considerable clinical potential", says Markland.

Another family of snake-venom anticoagulants-disintegrins-may also be useful clinically. Disintegrins disrupt integrins on the surface of platelets, preventing their normal interaction with the extracellular matrix and with other cells. Disintegrins are currently being tested as antitumour agents because they also interfere with the function of integrins on tumour cells, explains Markland. His group has tested a disintegrin from southern copperhead venom for activity against human mammary tumours in a mouse model. "Disintegrins inhibit tumour growth, and also angiogenesis and metastasis, probably because they prevent the normal function of integrins on endothelial cells." The team eventually hopes to take this work into clinical trials, but, says Markland, "that won't happen immediately. We may need to synthesise or modify the native snake-venom protein before starting human studies".

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Some venoms also contain components which stimulate blood clotting. A thrombin-like fraction, purified from the venom of the South American rattlesnake (Crotalus durissus terrificus), is being investigated for use in a fibrin tissue adhesive by Benedito Barraviera and Hamilton Stolf (State University of Sao Paulo, Botucatu, Brazil). The snake thrombin-like fraction "is much more potent than the bovine thrombin currently used" in fibrin adhesives, says Barraviera, and its use avoids the safety issues associated with the use of bovine or human thrombin (see Lancet 1997; 349: 334).

Meanwhile, Phil Griffiths, Doug Turnbull, and John Harris (all at Newcastle University, UK) are about to start a small trial to see if notexin, a phospholipase that attacks motor-nerve terminals and muscle cells, can reverse ptosis (drooping eyelids) in patients with rare inherited mitochondrial myopathies. "Skeletal muscle cells are badly affected in these diseases" and die as the patient ages, explains Harris, "but Turnbull and co-workers have found that the satellite cells between the muscle cells contain mostly normal mitochondria. When skeletal muscle is damaged by notexin, satellite cells divide to form replacement muscle cells and, because cell regeneration is accompanied by mitochondrial regeneration, the mitochondria in new muscle cells are in much better shape than in the old cells". Because ptosis is a result of muscle weakness in the small, easily accessible levator muscle of the eyelid, it is an ideal candidate for notexin therapy, adds Harris. "Someone with ptosis is effectively blind and, although there is a surgical treatment, this results in the eyelids being open constantly. Even partial restoration of the normal function of the levator muscle would provide a more comfortable alternative", he concludes.