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Explanation of timing of botulinum neurotoxin effects, onset and duration, and clinical ways of influencing them

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ABSTRACT

While the steps in the action of botulinum neurotoxin (BoNT) are well known, the factors underlying the timing of these steps are not fully understood. After toxin is injected into a muscle, it resides in the extracellular space and must be taken up into the nerve terminals. More toxin will be taken up if near the endplate. Toxin is distributed mainly by convection and there is likely little diffusion. Toxin that is not taken up will go into the general circulation where it may have a slight systemic effect. The uptake is activity and temperature dependent. Encouraging the unwanted muscle contractions after injection should be helpful. Cooling will decrease the uptake. The times for washout from the extracellular space and uptake of the toxin are not well established, but are likely measured in minutes. Toxin in the general circulation has a long half time. The time from injection to weakness is determined by how long it takes to get sufficient damage of the SNARE proteins to interfere with synaptic release. Toxins are zinc dependent proteases, and supplemental zinc may produce a greater effect. There will be weakness as long as there is residual toxin in the nerve ending.

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The botulinum neurotoxins (BoNTs) are commonly used for many different indications. The clinical effects are certainly well known, but a detailed explanation of all the phenomena is still lacking. In particular, while many of the steps in the action of the BoNTs are well understood, the factors underlying the timing of these steps are less so. In relation to effects at the neuromuscular junction, initial weakening does not occur for several days and the peak occurs in the order of several weeks. Effects subside at 2 months and strength generally returns to normal by 3 months. Improved knowledge of the physiology should have clinical implications to improve efficacy in the use of toxins. This article will review the sequential steps in toxin action, pointing out what is known and what is not, and will try to indicate clinical implications of these issues.

After toxin is injected into a muscle, it resides in the extracellular space and must be taken up into the nerve terminals. As this process occurs only at the endplate, clearly more toxin will be taken up if the injection is near the endplate. Endplates are generally located in the middle of muscle fibers, but as fibers are organized differently in different muscles, anatomical knowledge must guide the injector. Physiologically, the motor point is the place on the muscle where the stimulation intensity is least to evoke a muscle response. Sometimes this is the endplate zone, but sometimes not, so this is not reliable (Guzman-Venegas et al., 2014). By EMG criteria, endplate spikes certainly are indicative of being in the right place, but these cannot always be found. If the motor unit configurations show initial negative phases, this means that the muscle action potentials are arising near the recording needle, and the endplate must be nearby. High density surface EMG can also define the endplate zone (Lapatki et al., 2011). If attention is paid to injecting at the endplate, the effect will be greater (Delnooz et al., 2014; Gracies et al., 2009).

Toxin will be distributed in the muscle belly by means of convection, that is, the bulk movement of the fluid determined by the fluid volume and the force of the injection. Subsequently there might be diffusion; that is, spread from the initial site by Brownian motion determined by the concentration gradient and molecular size. Fascial boundaries between muscles do not appear to be significant barriers (Shaari et al., 1991), so nearby muscles can be affected depending on the accuracy of needle placement and the volume of the injection. Diffusion takes time, and there may not be much time because there is continuous washout from the extracellular space.

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BoNT in the muscle has been imaged by MRI (Elwischger et al., 2014). Toxin distributes along the long axis of muscle fibers and does not change much in a 10 min period. The volume of distribution is similar, but might be slightly less, in spastic versus normal muscle. In fact, as modeled in mouse muscle, the volume of distribution becomes rather quickly less (Fig. 1) (Tang-Liu et al., 2003). By two hours it is appreciably smaller and by 12 h, there is hardly any to be seen. The different marketed brands of BoNT exist in different forms and complexed with different amounts of protein, but the region of effect does not seem to differ if similar volumes are used for injection (Carli et al., 2009).

Taken together, the evidence seems fairly clear that the distribution is determined primarily by convection, which in practical terms is the volume of the injection.

As noted already, there is continuous washout from the extracellular space. The half-life may only be a few minutes, but is at

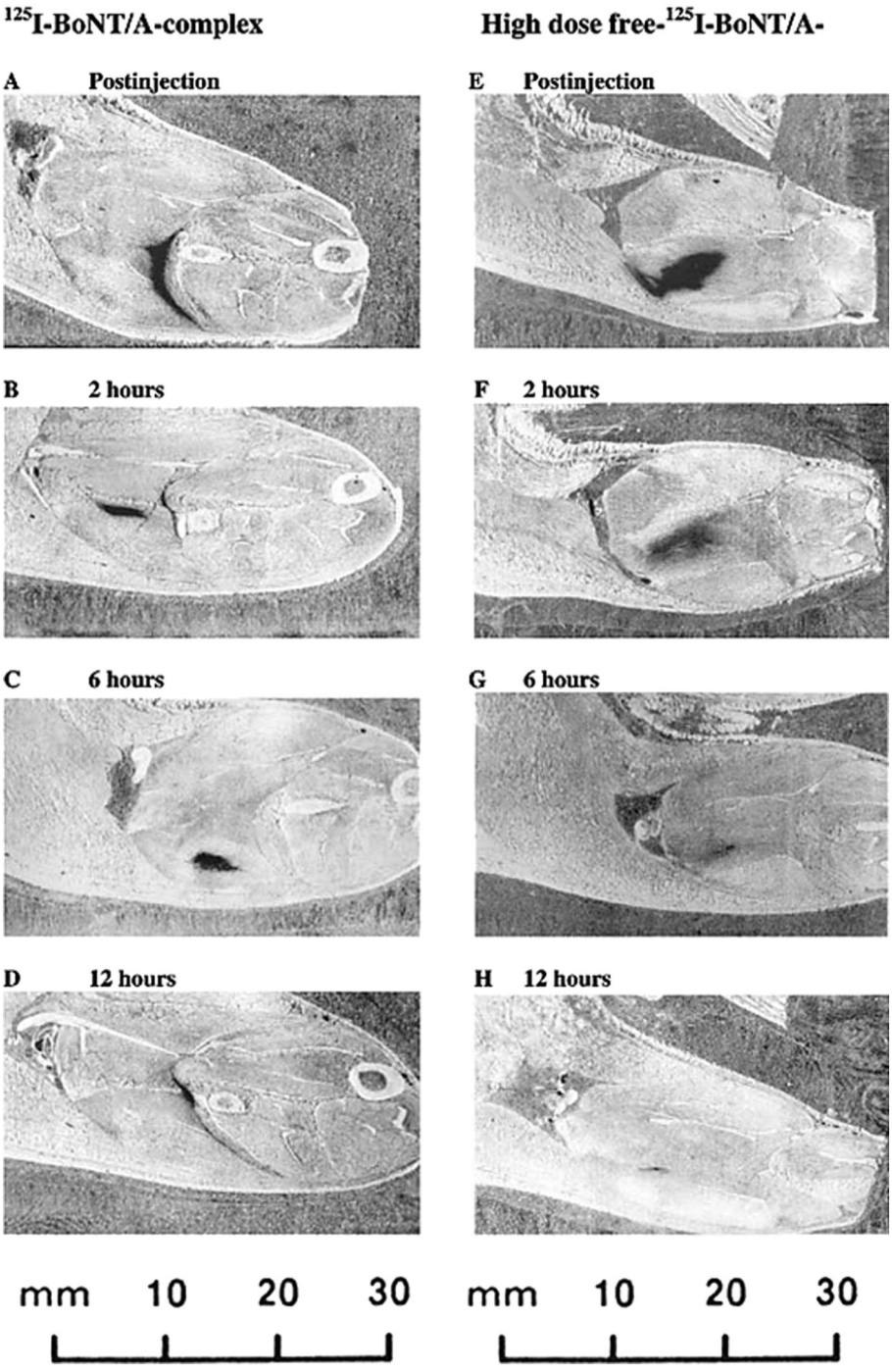

Fig. 1. Autoradiographs of sections through the gastrocnemius muscle injected with 125I-BoNT/A-complex, from four separate rats, (A) immediately after injection, (B) 2 h postinjection, (C) 6 h postinjection, and (D) 12 h postinjection. Sections correspond to the central plane of the injection and range from 5.6 to 8.3 mm below the surface of the preparation. Autoradiographs of sections through the gastrocnemius muscle injected with high-dose free-125I-BoNT/A, from four separate rats, (E) immediately after injection, (F) 2 h postinjection, (G) 6 h postinjection, and (H) 12 h postinjection. Sections correspond to the central plane of the injection and range from 3.6 to 4.9 mm below the surface of the preparation. From Tang-Liu et al. (2003) with permission.