

INJECTION PAIN OF BIOLOGICS - DOES IT HURT?

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Taking an injection may be an uncomfortable, frightening or painful experience, but it may also be a “no-big-deal” event with no negative feelings involved at all. For not so few people taking and feeling an injection is a signal and re-assurance that they have received the medication that keeps them well and it generates positive feeling. I have heard this from people ranging from haemophilia to cancer to diabetes. However, there are still many facets of injections that most people have some concerns with.

The intrusive nature of an injection involves many components and events.

Injection type: Typically physicians rate the “painfulness” of injections in the order Intradermal > subcutaneous > intramuscular > intravenous. However, there are several other injection types such as intravitreal or intracavernosal that has a physiology of their own

Injection site: This is important particularly for subcutaneous and intramuscular injections. Choosing the right area on your body for the injection will give the optimal physiological conditions for the injection, thickness of the subcutaneous tissue and underlying fat. However, it will also give you the best control of the injection which as a self-injecting patient could be very important to handle fear or discomfort.

The needle: Pushing a steel needle through skin is obviously an intrusion that could be painful. However, parameters such as needle thickness, tip cut or sharpness will greatly influence the perception of this intrusion. The needles used for injecting insulin today are around 0.25 mm thick whereas many monoclonal antibodies are injected with needles of 0.4 mm needle

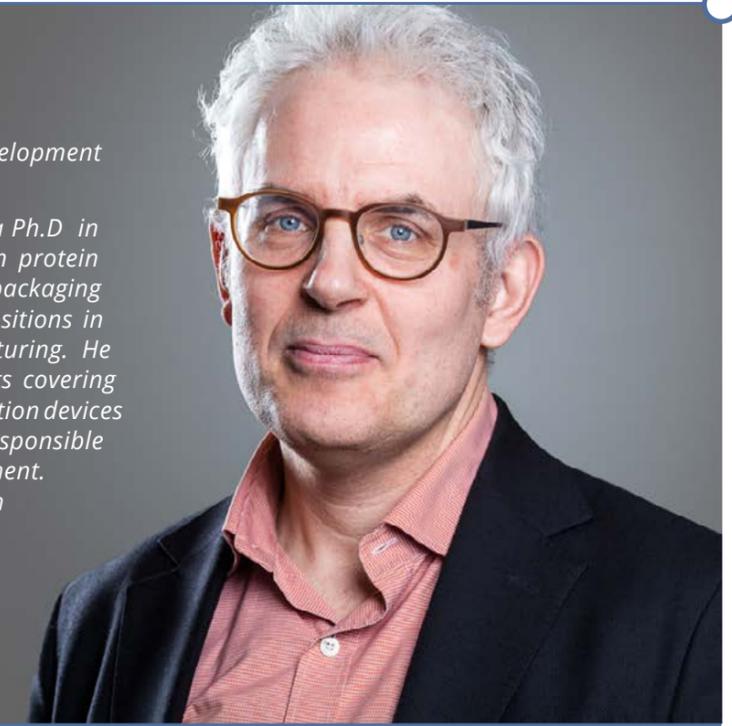
which is still quite thin. Also, the sharpness and cut of the needle tip has advanced considerably of the latest years introducing needles with multiple angles and shapes in the tip to reduce the impact in the injected tissue. Obviously, the choice of needle is dependent on the properties and volume of the solution to be injected. There are many products that could not be injected through a 0.25 mm needle within a reasonable time and without clogged needle etc.

Injection technique. How you hold the syringe when penetrating the skin and at what angle is obviously important to both optimize the physiology of the injection but also the perception. But the technical parameters starts before the actual injection. Pre-treating the injection site can be very important to improve the injection experience, both for children and adults. Simple procedures like pre-cooling the injection site with a cooler or applying a pain-reducing cream can be very efficient. There are now different stimulating devices which vibrates and distracts the injection in advance that can be quite efficient. Furthermore, typically many solutions for injections are refrigerated and warming or equilibrating the solution and syringe to room temperature before

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the injection is typically very useful to reduce any discomfort during the injection. In addition, the volume of injection is important, particularly for subcutaneous or intramuscular injections. Currently there is a perceived barrier of <1 mL for sc or im injections. It is worth to keep in mind that this volume limitation is primarily driven by the fact that a self-injecting person cannot really be expected to sit and inject for more than 30-60 seconds which it takes to inject 1 mL. If you have a larger volume you could consider dividing up in two injections instead, which happens in reality.

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The Drug solution: Typically, and well justified drug formulations are designed to maintain the quality of the drug product as main objective. Obviously, the formulators are aware of the physiology of the body and try to as much as possible adjust to solution properties to be compatible with the tissues and fluids it will meet and mix with. Making the solution isotonic or at least reasonably hypertonic by adding a suitable tonicity agent (typically sodium chloride or mannitol) is key to avoid haemolysis. Formulating a physiological pH (i.e. 7.4) may be more challenging due to poor stability of your drug at this pH and “non-physiological” pH may be needed to target in the

drug solution to have sufficient shelf life. However, using a low concentration of buffer may effectively reduce this issue as the body may neutralize the pH of the injected solution by its internal buffering system. Interestingly, with the introduction of many high concentration Monoclonal Antibodies and other protein therapeutics there has been findings that these high concentration protein solutions have a very good buffering capacity in their own and extra buffers may not even be needed. However, the buffered pH may still not be fully physiological. In addition, there are different stabilizing formulation components that may cause or reduce pain as well. It is a delicate task for the formulator to balance all these aspects when designing the product composition to have be injectable but have good stability at the same time.

In summary, “local tolerance” or perhaps “perception” of injections is an important aspect to carefully consider when designing products but also when designing treatment or procedure protocols. Although various types of injections have been used for more than 200 years there are still developments in this area. With the recent increase in use of biological therapeutics which are typically injected due to their high molecular weight this further emphasizes the needs for new technologies making the treatments acceptable and compliant ■

