

Clinical Experiences with needle-free Application (Jet-Injection) of Insulin and other Pharmaceuticals to be injected subcutaneously

A. Molecular Integrity of Insulin and Model Compounds after Jet-Injection

Publications of the last two decades generally demonstrate equivalent absorption of insulin (regular and/or NPH preparations) and Heparin resulting in similar peak plasma concentrations either with jet injection or conventional needle syringe [1,2,3,4,6,8,9,16]. The pharmacokinetic data obtained, indicate that jet injection does not modify the physical structure and bioactivity of these molecules. Some investigators, however, point out that needle-free administration of regular insulin or mixed regular/NPH insulin produces more rapid and less prolonged increases in plasma free insulin concentrations than does conventional subcutaneous injection. These findings suggest, that when switching from a syringe to a jet injector, insulin dose adjustment may sometimes become necessary. Own pharmacokinetic data following injection of a fast acting insulin analogue (LISPRO) with INJEX™ didn't show any differences compared to needle administration, neither in time to peak free plasma concentrations nor in total amount of free insulin [6].

Further pharmacokinetic findings from an independent clinical investigation with INJEX™ (M. Pfohl, Ruhr University Bochum, Presentation at the 35th Annual Meeting of the German Diabetes Association, Munich, June 2000) indicate a slightly faster time to peak concentration of a mixed regular/NPH insulin compared to needle administration with a Pen. The INJEX™ System proved to be more tissue-preserving [7,16] than the conventional injection method (see below).

Following jet-injection (INJEX™) of model compounds, like

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| a) | Vitamin B12 | - 1.350 Daltons |
| | Myoglobin | - 17.000 Daltons |
| | Ovalbumin | - 44.000 Daltons |
| | Immunglobuline G (bovine) | - 158.000 Daltons |
| | Thyroglobuline | - 670.000 Dalton (dimer) |
| b) | r-hgh | - 22.000 Daltons |
| | IGF-I | - 7.649 Daltons |
| c) | Interferon- α 2b | - 19.000 Daltons |
| d) | Various insulins | - 5000 to 6000 Daltons |

these molecules were analysed for their physical integrity and biological reactivity by SEC-HPLC, PAGE and immunoassays. The results indicate, that jet-injection with the INJEX™ System neither causes modifications in molecular structure, molecular weight, molecular charge nor in immune reactivity [5,10,11].

References:

1. Twice Daily Mixed Regular and NPH Insulin Injections with New Jet Injector Versus Conventional Syringes: Pharmacokinetics of Insulin Absorption (Halle, J.P. et al., DIABETES CARE, 1986; 9: 279-82)
2. Comparison of Plasma Insulin Profiles after Subcutaneous Administration of Insulin (Actrapid U 100) by Jet Spray and Conventional Needle Injection in Patients With Insulin-Dependent Diabetes Mellitus (Pehling, G.B. et al.; Mayo Clin Proc 59: 751-754, 1984)
3. Comparison of Insulin Levels (Humulin U-100) After Injection by Jet Stream and Disposable Insulin Syringe (Malone, J.I. et al., DIABETES CARE, Vol. 9 No. 6, 1986: 637-41)
4. Jet-Injected Insulin is Associated With Decreased Antibody Production and Postprandial Glucose Variability When Compared With Needle-Injected Insulin in Gestational Diabetic Women (Jovanovic-Peterson, L. et al., DIABETES CARE, Vol. 16, No. 11, 1993: 1479-84)
5. INJEX™: Retention of Structural/Potency Characteristics of Injectable Drugs and Model Compounds (Equidyne Technical Report, December 1998)
6. INJEX™ Injector Efficacy Study, (Technical Report 006, J B & Associates, August 1999)
7. Erste Erfahrungen mit Insulininjektoren - Vergleichsstudie zwischen INJEX™ und Insulin Pens, (Pfohl, M. et al.; DDG Tagung 03.06.2000, München, filed for publication)
8. INJEX™, Retention of Structural/Potency Characteristics of Insulins, (Techn. Report 105, Vision Biotechnology Consulting, April 2000)
9. Subkutane Applikation von Heparin mit einem Injektor (J. Harenberg et al.; Dtsch. med. Wschr. 107, 1982, 497-500)
10. Technology Evaluation Report for Hypex (= INJEX) Injector (Genentec, Inc., San Francisco 1996)
11. Bestimmung der Aktivität von Interferon-alpha nach nadelloser Applikation mit dem INJEX™-System in vitro und in vivo (Bericht Fraunhofer Institut für Toxikologie und Aerosolforschung, Hannover, Sept. 2000)

B. Depth of Penetration and Dispersion of a Dye following Jet-injection

Pre-clinical studies with different devices to determine acute damage of the injected area by histological examination following jet injection were published. It was demonstrated that jet injected fluids will follow the path of least resistance and did not pass into the substance of bone, into the media of blood vessels, or into the fiber substance of nerve trunks [12]. To our knowledge injuries of this kind are not reported in the current literature. One case report even showed significant recession of insulin induced lipodystrophy [14].

In an own investigation, radio-dense saline solution (0.3 ml) was injected with either a conventional needle syringe or INJEX™. Radiographs of the injected area (triceps of upper arm of a healthy adult volunteer) taken parallel and perpendicular to the line of injection did not show any difference between the two modes of administration. Depth of penetration was strictly limited to the subcutaneous tissue. Conclusion: Jet injection of saline solution provides penetration and infiltration comparable to that produced by needle injection[15].

In addition, a body of histologic findings from an ex-vivo study with INJEX™ clearly demonstrated the tissue preserving properties of the needle-free injection technique (Mediport Berlin; August 2000). The data obtained, show under a fully intact epidermis a deposit cone in the subcutaneous fatty tissue without remarkable oedema formation[16].

The INJEX™ is a spring-loaded variable-dose injector to which a disposable plastic ampoule attaches, containing the medication. The activated trigger releases the spring propelling the liquid drug under high velocity through a micro-orifice (0.17 mm) in the ampoule tip. The jet stream of medication traverses the skin (140 msec) and the drug disperses into the subcutaneous adipose tissue. Spring pressure and orifice diameter are designed for a depth of penetration of about 3 to 9 millimetres. Thus, injection into the intramuscular tissue (accidental hypoglycaemia in diabetics!) is virtually impossible (a study in 69 diabetic children at the Robert Debré University Hospital, Paris, France, revealed that - contrary to all expectation - 30% of the study population routinely performed intramuscular insulin-injections instead of subcutaneous ones; Diabetes Care, Vol. 19, No. 12, 1996).

References:

12. Studies on tissue penetration characteristics produced by jet injection (Bennett, C.R. et al., JADA, Vol. 83 Sept. 1971: 625-29)
13. Subcutaneous or Intramuscular Injections of Insulin in Children: Are we injecting where we think we are? (Polak, M. et al.; DIABETES CARE, Vol. 19, No. 12, 1996: 1434-35)

14. Human Insulin-Induced Lipoatrophy: Successful treatment using a jet-injection device (Logwin, S. et al., DIABETES CARE Vol. 19. No.3, 1996: 255-56)
15. Gewebeinfiltration nach automatischer Injektion mit INJEX™ System im Vergleich zu konventioneller Nadeltechnik (Rösch Techn. Report, August 1999)
16. Bestimmung der histologischen Verteilung eines Farbstoffs und Aufnahme einer Resorptionskinetik von Heparin nach Injektion mit dem INJEX™-System (Mediport GmbH, Berlin, August 2000)

C. Sterility Issues

Regulatory shift to safer injection technology in the US is a result of more than one million accidental needle-stick injuries reported per year, causing severe infections of at least 60.000 hospital employees during the last decade (average of 1 AIDS infection/week). Therefore, the federal Needlestick Safety and Prevention Act was recently passed, imposing the use of safety engineered syringes, only.

In home care (e.g. Diabetes mellitus), so-called "pens" for application of insulin are generally accepted. Although aspiration of blood or tissue fluids into the pen cartridges is reduced to a minimum, it is advised to use one pen only for each individual in order to avoid infections.

The INJEX™-system uses sterile injection ampoules for single use. These are filled through a disposable, sterile adapter, which is to be discarded with the vial or the pen-cartridge when the medication is used up. As the ampoules are filled without any contact to the skin, contamination of the adapter by blood or body fluids is excluded. Contamination through the environment is prevented by closing the adapter immediately after filling the ampoule. In order to further minimise potential contamination, medications which are delivered in multidose vials must by law contain a proper preservative (in the case of insulin m-cresol or methyl-4-hydroxy-benzoate).

INJEX™ got CE-mark approval for subcutaneous administration of drugs in September 1999 and is marketed since January 2000 in Germany.