

### Introduction

To claim safety and efficacy of the INJEX™ system studies were performed to compare pharmacokinetics of three drugs following the application with the INJEX™ injector.

### Objective

To evaluate the injection of liquid medicines with the INJEX™ injector studies were conducted by administering insulin, recombinant human growth hormone, and heparin to humans and animals and compared to kinetics following pen injections and injections with conventional syringes

### Material and Methods

- I. Report: Comparison of Blood Glucose and Insulin Kinetics following Needle-free and Pen injection of Insulin
- II. Report: Comparative pharmacokinetics of recombinant human growth hormone following administration with a needle-free injection device Genotropin® INJEX™ and a conventional needle and syringe
- III. Study Report: Investigation of Penetration Depth and Histological Dispersion of Dye injected with the INJEX™ – Jet Injector

### Results

- I. Report: Comparison of Blood Glucose and Insulin Kinetics following Needle-free and Pen injection of Insulin

To investigate the application of insulin with the INJEX™ injector kinetics of blood glucose and insulin were studied in 10 patients over a period of 6 hours after administering insulin with the INJEX™ needle-free injection system. The results were compared with those obtained after insulin injection with a conventional pen system.

No significant differences were noted between the different injection systems during the 2-way analysis of variance or at any time of the measurement period (s. Fig.1, tab. 1).

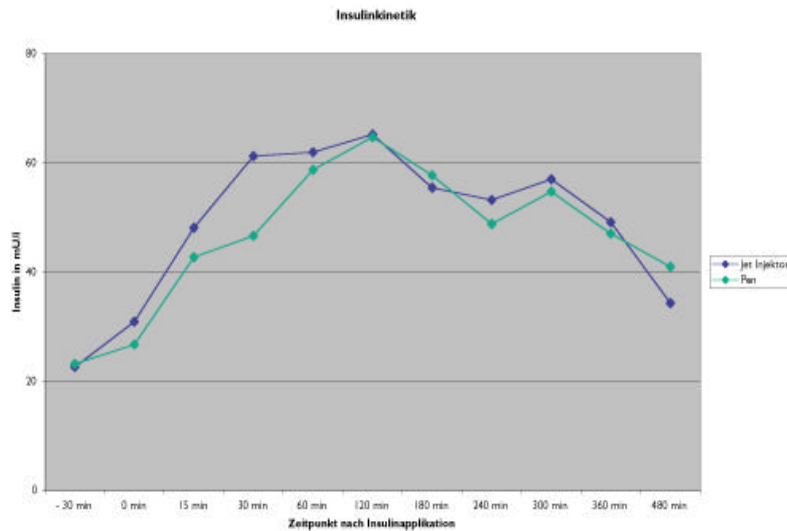


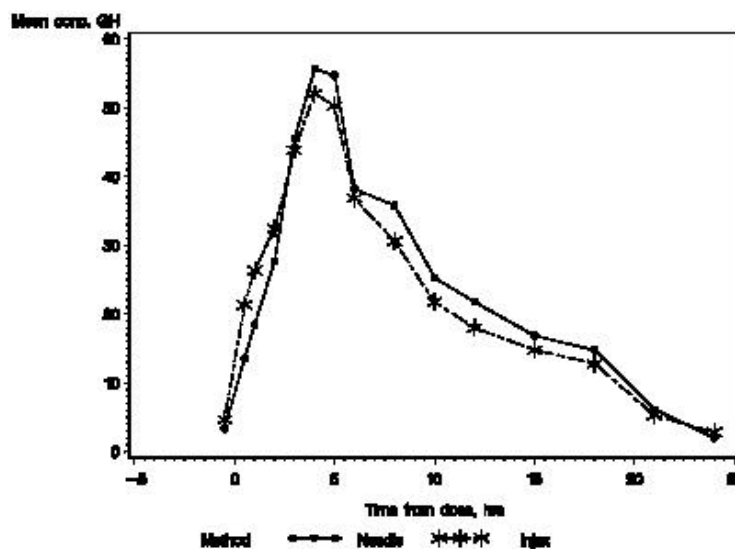
Figure 1: Comparison of concentration profiles after administration of insulin with the INJEX™ injector and pen system as function of time

**Table 1:** Plasma concentrations of 10 patients with insulin-treated diabetes mellitus before and after insulin was injected using the insulin pen or the INJEX.

time [min]	INJEX™ Injector	Insulin Pen
- 30 min	22.6 ± 7.9	23.2 ± 13.2
0 min	30.9 ± 12.4	26.7 ± 16.7
15 min	48.1 ± 18.5	42.7 ± 25.4
30 min	61.2 ± 39.7	46.6 ± 24.9
60 min	61.9 ± 28.7	58.7 ± 37.6
120 min	65.2 ± 36.1	64.7 ± 38.4
180 min	55.4 ± 27.5	57.7 ± 23.3
240 min	53.2 ± 21.5	48.8 ± 24.4
300 min	57.0 ± 38.9	54.7 ± 42.0
360 min	49.1 ± 30.9	47.0 ± 29.5
480 min	34.3 ± 12.2	41.0 ± 18.9

## II. Expert Report on the Clinical Documentation for Genotropin® INJEX™

The pharmacokinetics of the human growth hormone were determined in 18 healthy volunteers after administration of 0.3 ml of Genotropin® 12 mg/ml by the INJEX™ injector or conventional syringe. To ensure consistency in drug administration one research nurse carried out all injections in each subject. As depicted in figure 2 the mean concentration- time profiles were similar for both injection methods.

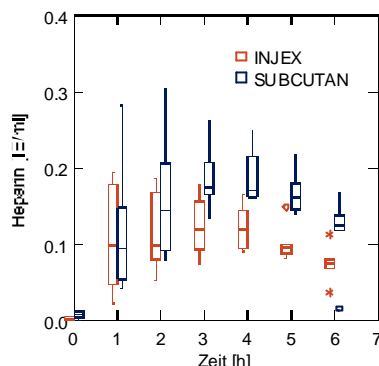


**Figure 2:** Comparison of concentration profiles after administration of the growth hormone with the INJEX™ injector and conventional syringe as function of time

## III. Study Report: Investigation of Penetration Depth and Histological Dispersion of Dye injected with the INJEX™ – Jet Injector

The investigations for the determination of the absorption of HMW heparin following administration with the INJEX™ System and a conventional needle system were carried out in the isolated haemo- perfused forelimb of the pig (Fig.

3). The injection volume of both systems was 0.3 ml (1500 I. U.). The mean maximum plasma concentration in the pig limb achieved with the INJEX™ System amounted to 0.124 IU/ml (S.D. 0.041).



**Figure 3:** Comparison of concentration profiles after administrating heparin to the perfusate with the INJEX™ injector and conventional syringe versus time.

## Discussion

I. No statistically significant differences in terms of blood glucose and insulin kinetics were observed between the two insulin application systems over the measurement periods. On average, the needle-free injection system was assessed as satisfactory with regard to preparation, change of cartridge and dose accuracy.

II. The data showed that the pharmacokinetics of recombinant human growth hormone (Genotropin®) either after administration via the INJEX™ needle-free device or a conventional syringe are similar. Furthermore, bio-equivalence was confirmed between the two administration methods as the 90% CI of the treatment ratio for log-transformed AUC<sub>0-8</sub> of human growth hormone was within the equivalence range of 80% to 125%.

III. The absorption tests carried out in the study demonstrated that the absorption after injection of HMW heparin with the INJEX™ system is comparable to that after injection with a conventional needle system. However, the concentrations determined remained somewhat below those obtainable with the needle system. The maximum concentration was determined after 3.- 4 hours and is comparable to those reported in the literature (Harenberg et al., 1982; Black et al., 1978).

## Conclusion

Due to the results obtained by investigating the pharmacokinetics of three drugs in humans and animals it can be concluded that the injection of liquid pharmaceuticals with the INJEX™ injector is equivalent to those performed with conventional systems.

The absorption kinetics of heparin observed in the study described a similar time dependent behaviour for the INJEX™ system and the conventional syringe. Further, the results are consistent with those reported in the literature performed with a CO<sub>2</sub> gas injector (Harenberg and co-workers).

Administering Genotropin® using the INJEX™ needle-free device was judged as bio- equivalent to Genotropin® administered by conventional subcutaneous injection.

Using the INJEX™ needle-free injection system, comparable control of blood glucose to that of insulin injection via pen system was obtained.