RÉSUMÉ

OBJECTIF: Préciser les paramètres de la pentoxifylline et de ses métabolites suivant l'administration orale (bid et tid) de doses multiples chez des patients présentant une dysfonction rénale.

DEVIS EXPÉRIMENTAL ET LIEU DE L'ÉTUDE: Étude ouverte, randomisée, en chassé-croisé et avec groupes parallèles, réalisée dans un centre de recherche clinique.

PATIENTS: Les volontaires ont été regroupés en fonction de la valeur de leur clairance à la créatinine (Cl_{cr}) estimée à partir d'une collecte urinaire de 24 heures: groupe I = Cl_{cr} > 80 mL/min (n = 9); groupe II = Cl_{cr} 30–80 mL/min (n = 6); et groupe III = Cl_{cr} < 30 mL/min (n = 10).

MÉTHODES: La pentoxifylline a été administrée à raison de 400 mg bid ou tid les jours 1 à 7 et 400 mg tid ou bid les jours 14 à 20 avec une période de retrait de 7 jours. Des prises de sang ont été effectuées aux jours 1, 7, et 20. Les échantillons sanguins ont été analysés quant à leur contenu en pentoxifylline et en métabolites de la pentoxifylline (M-I, M-IV, et M-V) par chromatographie liquide en phase gazeuse.

MESURES DE L'EFFET: Les valeurs de C_{max}, t_{max}, $C^{éq}_{moy}$, et $SSC_{éq}$ ont été déterminées. L'analyse de variance, le test de *t*, et al régression linéaire ont été utilisés avec un valeur de $p < 0.05$.

RÉSULTATS: Les rapports $SSC_{éq}$ (tid):$SSC_{éq}$ (bid) pour la pentoxifylline et $SSC_{éq}$ (bid et tid) pour M-I ne se sont pas avérés significativement différents entre les groupes ($p > 0.6$). Des différences significatives ont cependant été observées en ce qui concerne la C_{max} de M-IV et M-V, la $SSC_{éq}$, la $C^{éq}_{moy}$, et les rapports $SSC_{éq}$ (M-IV:pentoxifylline) entre les groupes ($p < 0.05$). Une modification de la posologie de tid à bid a produit des changements significatifs au niveau de la $C^{éq}_{moy}$ de M-IV et M-V chez les individus ayant une fonction rénale normale ou une dysfonction rénale modérée mais pas chez les individus ayant une dysfonction rénale grave.

CONCLUSIONS: La dysfonction rénale n'entraîne pas d'accumulation significative de pentoxifylline ou de M-I après l'administration bid et tid de doses multiples. Cependant, les métabolites M-IV et M-V s'accumulent de façon significative lors d'insuffisance rénale. Une modification de la posologie (400 mg bid si insuffisance rénale modérée et 200 à 400 mg qd si insuffisance rénale grave) et un monitorage clinique étroit sont recommandés et ce, jusqu'à ce que les interactions pharmacologiques complexes entre la pentoxifylline et ses métabolites soient mieux définies.

ALAIN MARCOTTE

General Medicine

PAIN ASSESSMENT OF SUBCUTANEOUS INJECTIONS

Jan T Jørgensen, Janne Rømsing, Mette Rasmussen, Jørn Møller-Sonnergaard, Lisbeth Vang, and Lise Musæus

OBJECTIVE: To compare injection pain after subcutaneous administration of four different solution volumes.

DESIGN: Double-blind, randomized, prospective, multiple crossover study.

SETTING: Steno Diabetes Centre, Gentofte, Denmark.

PARTICIPANTS: Eighteen healthy volunteers, 9 women and 9 men, aged 21–30 years.

METHODS: The subjects were injected with four different volumes (0.2, 0.5, 1.0, 1.5 mL) of NaCl 0.9%. The study was performed on 2 days with a 1-week washout period between the study days. On each study day the subjects received four injections in each thigh. To evaluate the validity of our pain assessing model the subjects received eight injections of 0.5 mL on one of the study days. Pain assessment was done immediately after each injection using both a 10-cm visual analog scale (VAS) and a six-item verbal rating scale (VRS).

RESULTS: A significant difference in pain score on both the VAS ($p < 0.05$) and the VRS ($p < 0.01$) was seen between the four injection volumes. The pain was significantly increased with volumes of 1.0 and 1.5 mL. No significant difference in injection pain could be detected between 0.2 and 0.5 mL and between 1.0 and 1.5 mL. No significant period or carryover effect could be detected in the study. A significant correlation between the pain score on the VAS and the pain score on the VRS was found ($r = 0.79$, $p < 0.0001$).

CONCLUSIONS: The pain of a subcutaneous injection is related to injection volume in the thigh. The results show that increasing the volume from 0.5 to 1.0 mL increases the pain significantly. The findings from this study should be considered when injection preparations for subcutaneous administration are formulated. The volume should generally be less than 1.0 mL if injected into the thigh.

Ann Pharmacother 1996;30:729-32.

Jan T Jørgensen PhD, Research Fellow, Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen, Denmark
Janne Rømsing PhD, Assistant Professor, Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen
Mette Rasmussen PhD, Associate Professor, Department of Pharmaceutics, The Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark, FAX +4535371277
Jørn Møller-Sonnergaard PhD, Associate Professor, Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen
Lisbeth Vang RN, Steno Diabetes Centre, Gentofte, Denmark
Lise Musæus RN, Director of Nursing, Steno Diabetes Centre, Gentofte
Reprints: Mette Rasmussen PhD

The study was supported by Novo Nordisk A/S, Gentofte, Denmark.

INJECTION PAIN IS A PROBLEM for many patients in relation to the daily subcutaneous administration of different medications, such as insulin and growth hormone. The pain induced by a subcutaneous injection depends on several fac-

tors, such as choice of preservative in the solution,[1] needle size (gauge),[2] type of needle insertion,[3] and injection site.[4,5] Other factors, such as the pH and the osmolality of a solution, may also contribute to injection pain.

The volume of the solution may also have an influence on injection pain.[6,7] Only one previous study[7] has focused on this subject. In that study, five different volumes of insulin which ranged from 0.025 to 0.5 mL were compared. No significant differences in pain perception were seen between these volumes. For comparison of injection pain, a 21-cm visual analog scale (VAS) was used,[7] which is less reliable than a 10- or 15-cm VAS.[8]

The purpose of our study was to compare the injection pain of subcutaneous administration of four different volumes ranging from 0.2 to 1.5 mL. For measurement of the injection pain, a 10-cm standard VAS and a 6-item verbal rating scale (VRS) were used.

Methods

SUBJECTS

Eighteen healthy volunteers (9 women, 9 men), 21–30 years old (mean 25.2), weighing between 51.8 and 95.6 kg (mean 73.1) were included in the study. Based on weight and height, the body mass index (BMI) was calculated according to the formula [(body weight in kilograms) ÷ (height in meters)^2].[9] The BMI ranged from 19.4 to 27.9 kg/m^2 (mean 23.5). The subjects were instructed not to take any analgesics or consume any alcohol during the 48 hours prior to the study. Before initiation the protocol was approved by the Regional Ethics Committee, and written informed consent was obtained from each subject.

PROTOCOL

This was a double-blind, randomized, multiple crossover study, in which the injection pain of four different volumes (0.2, 0.5, 1.0, 1.5 mL) of NaCl 0.9% was compared. The syringes were covered with opaque tape. The injections were given subcutaneously by two diabetes nurses using a conventional 2-mL disposable syringe mounted with a 27-gauge needle (Neolus Terumo, 27 G × 3/3″). For each subject all injections were given by the same nurse. The study was done on 2 days with a 1-week washout period between the study days. On each study day the subjects received four injections in each thigh (Figure 1). Both the lateral and the medial positions were used. For each thigh, two injections were given proximally and two distally. According to the randomization code, each of the four volumes was given once proximally and once distally. On each of the two study days the subjects received either 0.5 mL in all eight injection sites, or four different injection volumes twice — once distally and once proximally. The assessment of the injection pain was done immediately after each injection using both a 10-cm VAS and a six-item VRS. The VRS was categorized as follows: no pain, mild pain, moderate pain, severe pain, very severe pain, and worst possible pain. The extremes on the VAS were no pain and worst possible pain.

The VAS and the VRS data were analyzed with the Wilcoxon test, the Mann-Whitney test, and the Kruskal–Wallis test. The VAS and VRS data were compared by means of the Spearman rank correlation test.

Figure 1. The four injection sites on the thigh.

Results

The pain scores resulting from the VAS and the VRS for all volunteers following injection of the four different volumes are shown in Figures 2 and 3, respectively. A significant difference in pain score on both the VAS ($p < 0.05$) and VRS ($p < 0.01$) was seen among the four volumes. When examining the individual injection volumes in detail, significant differences were found between 0.5 and 1.0 mL and between 0.5 and 1.5 mL. No significant difference was seen between 0.2 and 0.5 mL or between 1.0 and 1.5 mL.

The validity of our pain assessing model was tested using a volume of 0.5 mL in all eight injection sites. The individual pain scores from this volume did not show any significant trend toward decrease or increase in pain score with the eight injections. Furthermore, the comparison between pain scores on the first and the second injection day showed no significant difference. No significant period or carryover effect could be detected.

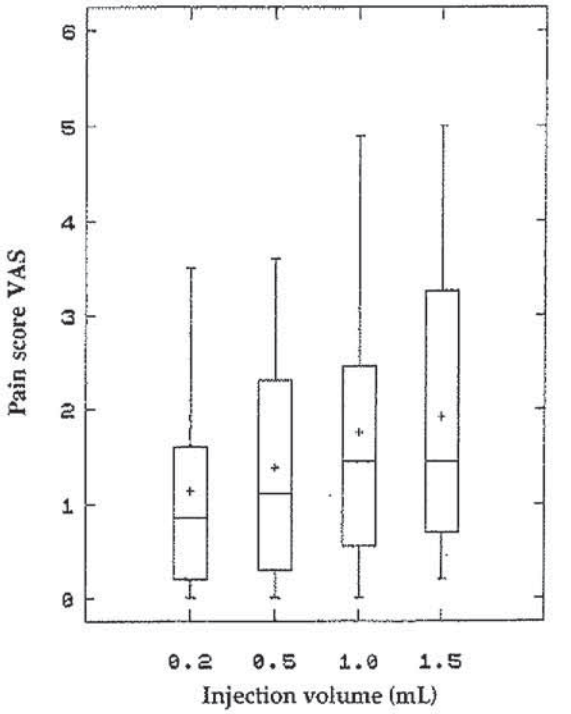

Figure 2. Multiple box-and-whisker plot based on visual analog scale (VAS) pain scores from the 18 volunteers following injection of the four volumes. For each volume, the box encloses the middle 50% of the VAS data, and the whiskers indicate minimum and maximum values. A cross indicates the mean and a horizontal line the median. (Kruskal–Wallis test, $p < 0.05$).

The pain scores from the two scales were compared. A statistically significant correlation between the pain scores on the VAS and the pain scores on the VRS was found ($r = 0.79$, $p < 0.0001$).

Discussion

To our knowledge this study is the first to demonstrate that the pain of a subcutaneous injection is related to the solution volume. Only one study[7] has previously dealt with this subject, but failed to show any correlation. The main reasons for this may be that the largest volume injected was 0.5 mL and that a nonstandardized VAS was used. The results from our study show that pain is significantly increased at an injection volume greater than or equal to 1.0 mL.

The study was carefully designed to rule out any contribution to injection pain from known factors such as needle size, preservative, and injection mode.[1-3] All injections of the NaCl 0.9% were performed by trained diabetes nurses using syringes mounted with a 27-gauge needle. The volumes in the range from 0.2 to 1.5 mL were chosen because this interval was regarded as being clinically relevant for subcutaneous injections. It is also known that injection pain varies with the injection site.[4,5] A previous study in insulin-dependent diabetic patients showed that pain was significantly greater distally on the thigh compared with the proximal position.[5] To avoid any systematic errors in the study design, the randomization was performed in such a way that each of the four different volumes was injected once proximally and once distally.

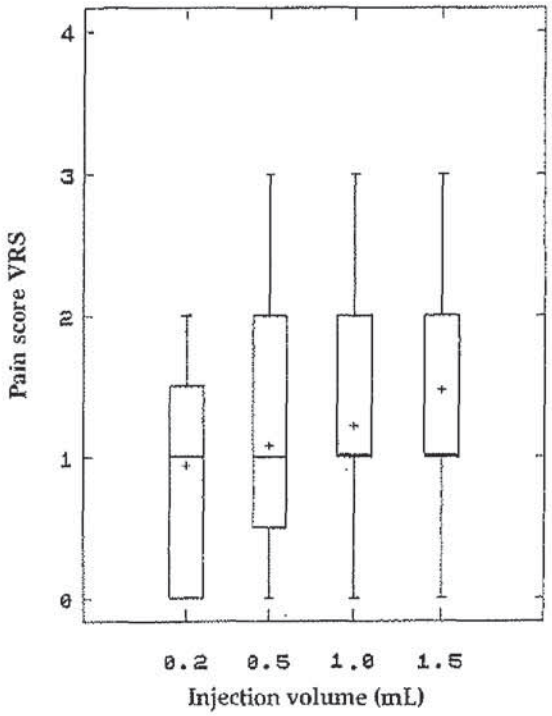

Figure 3. Multiple box-and-whisker plot based on verbal rating scale (VRS) pain scores from the 18 volunteers following injection of the four volumes. For each volume, the box encloses the middle 50% of the VRS data, and the whiskers indicate minimum and maximum values. A cross indicates the mean and a horizontal line the median. (Kruskal–Wallis test, $p < 0.01$).

To assess the validity of our pain-assessing model, 0.5 mL was administered to the volunteers at all eight injection sites on one of the two study days. Using these data we showed that there was no significant period or carryover effect. The 0.5 mL volume was chosen because it was regarded as being a clinically relevant injection volume. The BMI from the individual subjects can also be regarded as being representative for the normal population. Our model proved to be reliable for healthy subjects and valid for the purpose of this study. The correlation between the pain scores of the VAS and the VRS was high, indicating that the subjects had understood and used the pain scales correctly.

Since compliance is a problem in many types of medical therapy, issues relating to compliance should be considered during drug development.[3] One way to improve compliance could be through an improvement in patient convenience. From this point of view, the volume of a subcutaneous injection should be less than 1.0 mL. We therefore recommend that the results from this study be considered when injection preparations for subcutaneous administration are formulated.

Summary

The pain of a subcutaneous injection is related to the injection volume in the thigh. The results show that increasing the volume from 0.5 to 1.0 mL increases the pain significantly. In order to optimize patient convenience in relation to subcutaneous administration, the results from this study should be considered in relation to the formulation of injection fluids. The volume should generally be less than 1.0 mL if injected into the thigh. ≃

We thank pharmacy assistant Ruth Hansen, pharmacy student Ulla S Jensen, and pharmacy student Mette Munk-Petersen for technical assistance and advice, and medical writer Noëlle Holten Pind for linguistic advice. We also thank chief physician Hans-Henrik Parving, Steno Diabetes Centre, for his support.

References

1. Bridges A, Stirling H, McDowell J, Jensen S, Jørgensen JT, Kelnar C. Double-blind study to compare the local tolerance of three different solvents used to reconstitute growth hormone (abstract). Presented at the British Pharmacological Society Meeting, London University College, London, England, December 17–19, 1991.
2. Coley RM, Butler CD, Beck BI, Mullane JP. Effect of needle size on pain and hematoma formation with subcutaneous injection of heparin sodium. Clin Pharm 1987;6:725-7.
3. Jørgensen JT. Improvement of patient convenience in treatment with growth hormone. J Pediatr Endocrinol 1994;7:175-80.
4. Lee DM. How painful is intensive insulin injection therapy? Z Gesamte Inn Med 1992;47:266-9.
5. Christiansen JS, Sorensen JP, Hansen B, Christensen T. A double blind, randomized study on the degree of pain on penetration by Insuject and Novopen needle either proximally or distally of the thigh (abstract). Presented at 8th Workshop of the AIDSPIT Study Group, Igls, Austria, January 29–31, 1989.
6. Jørgensen JT, Mortensen HB, Jørgensen JOL. Patient acceptance of Nordiject: a new drug delivery system for growth hormone. DICP Ann Pharmacother 1991;25:585-8.
7. Chantelau E, Lee DM, Hemmann DM, Zipfel U, Echterhoff S. What makes insulin injection painful? BMJ 1991;303:26-7.
8. Seymour RA, Simpson JM, Charlton JE, Phillips ME. An evaluation of length and end-phrase of visual analog scales in dental pain. Pain 1985; 21:177-85.
9. Olefsky MJ. Obesity. In: Braunwald E, Isselbacher JK, Petersdorf RG, Wilson JD, Martin JB, Fauci AS, eds. Harrison's principles of internal

medicine. 11th ed. New York: McGraw-Hill Book Company, 1987: 1671-6.

EXTRACTO

OBJETIVO: Comparar el dolor asociado a la inyección subcutánea de cuatro volúmenes distintos de solución isotónica de cloruro de sodio.

DISEÑO: Estudio en doble ciego, aleatorio, prospectivo, de dosis múltiples, y cruzado.

ESCENARIO: Centro Diabético Steno, Gentofte, Denmark.

MÉTODOS: Se inyectaron 4 volúmenes distintos (0.2, 0.5, 1.0, y 1.5 mL) de solución isotónica de cloruro de sodio (isotonic sodium chloride, 9 mg/mL, DAK) a 18 voluntarios sanos. El estudio se realizó en 2 días separados uno de otro por una semana libre de la administración de las soluciones de estudio. En cada uno de los días de estudio, los voluntarios recibieron 4 inyecciones en cada muslo. Para determinar la validez del modelo de evaluación de dolor utilizado los voluntarios recibieron, bien sea un volumen de 0.5 mL en cada muslo o 4 volúmenes distintos de inyección por duplicado. La evaluación de dolor se realizó inmediatamente después de cada inyección usando una escala analógica visual (EAV) de 10 cm de longitud y una escala de clasificación verbal (ECV) de 6 elementos.

RESULTADOS: Se observó una diferencia significativa entre los 4 volúmenes de inyección con respecto al dolor reportado usando la EAV ($p < 0.05$) y la EVC ($p < 0.01$). El dolor se incrementó con el volumen de inyección de 1.0 mL y 1.5 mL. No se detectaron diferencias significativas en dolor entre los volúmenes de 0.2 y 0.5 mL y los volúmenes de 1.0 y 1.5 mL. Tampoco de detectó influencia del tratamiento precedente. Hubo una correlación significativa en cuanto a dolor entre la EAV y la EVC ($r = 0.79$, $p < 0.0001$).

CONCLUSIONES: Se concluye que el dolor asociado a la inyección subcutánea de una solución está relacionado al volumen de inyección en el muslo. Los resultados demuestran que el incrementar el volumen de inyección de 0.5 mL a 1.0 mL incrementa el dolor significativamente. Los hallazgos de este estudio deberían ser tomados en consideración cuando se formulen preparaciones parenterales de administración subcutánea. Se recomienda que el volumen de inyección sea menor de 1.0 mL cuando se inyecta en el muslo.

ENCARNACIÓN C SUÁREZ

RÉSUMÉ

OBJECTIF: Comparer la douleur résultant de l'injection sous-cutanée de quatre volumes différents de liquide.

DEVIS EXPÉRIMENTAL: Étude prospective, croisée pour les quatre volumes, randomisée, et à double-aveugle.

LIEU DE L'ÉTUDE: Steno Diabetes Centre, Gentofte, Danemark.

PARTICIPANTS: Dix-huit volontaires sains, 9 hommes et 9 femmes, âgés de 21 à 30 ans.

MÉTHODOLOGIE: On a injecté aux participants quatre volumes différents de solution saline isotonique (0.2, 0.5, 1.0, et 1.5 mL). L'étude a été faite sur 2 jours séparés d'un intervalle d'une semaine et tous les sujets ont reçu, à chaque jour, quatre injections sur chacune des deux cuisses. Afin de vérifier la validité du modèle choisi pour l'évaluation de la douleur, chaque participant a reçu huit injections de 0.5 mL au cours de l'une des deux journées d'étude. L'évaluation de la douleur était faite immédiatement après chaque injection en utilisant une échelle visuelle analogue (EVA) de 10 cm et une échelle verbale (EV) comportant six termes.

RÉSULTATS: Une différence significative a été détectée entre les volumes à l'étude selon les deux modalités d'évaluation utilisées (EVA, $p < 0.05$; et EV, $p < 0.01$). La douleur était significativement plus importante avec les volumes de 1.0 et 1.5 mL. Les auteurs n'ont pas détecté de différence significative entre les volumes de 0.2 et 0.5 mL de même qu'entre ceux de 1.0 et 1.5 mL. Il n'y a pas eu non plus de différence attribuable au facteur temps. Les auteurs ont trouvé une bonne corrélation entre les deux échelles utilisées lorsqu'ils en ont comparé les résultats ($r = 0.79$, $p < 0.0001$).

CONCLUSIONS: La douleur ressentie après une injection sous-cutanée dans la cuisse serait reliée au volume injecté. Les résultats ici montrent que passer d'un volume injecté de 0.5 à 1.0 mL augmente significativement la douleur. Les auteurs suggèrent que cette étude soit prise en considération par l'industrie pharmaceutique au moment de formuler les liquides destinés à l'injection sous-cutanée. Au niveau de la cuisse, le volume devrait généralement être inférieur à 1.0 mL.

MICHÈLE PLANTE