(Received February 5, 2001; Accepted March 23, 2001)

Coring is reported to occur because rubber pieces are shaved off from a rubber stopper when a needle is inserted into the rubber stopper of transfusion liquid formulation. We verified whether coring really occurs in insulin vials of self-injecting patients. We collected insulin cartridges from 30 hospitalized patients and used the primary injection (trial injection), the secondary injection and the cartridge remaining preparation as samples. We observed the rubber pieces using a microscope and measured the shape, number of pieces. The occurrence rate of coring was 73% for the primary injection, 47% for the secondary injection and 97% for the cartridge remaining preparation. The rubber pieces in the primary injection and the secondary injection which went through the needle are mostly in aggregate shape and the rubber pieces in the cartridge remaining preparation which did not go through the needle are mostly in needle-like shape. A number of small rubber pieces are found in both the primary injection and the secondary injection, indicating a high possibility that rubber pieces may be injected under subcutaneous tissue. The coring is considered to occur because needles are repeatedly inserted and rotated at the same spot. It is required to improve the structure to mount a needle to the pen-type injector in future. Coring is a very serious problem from the medical and pharmaceutical points of view. Further study should be made on the implication to latex allergy and lipodystrophy.

Key words——insulin; coring; needle; vial; diabetes

INTRODUCTION

The pen-type insulin injector (hereunder referred to as ''pen-type injector'') has been developed so that patients can mount and self-inject insulin from cartridges (hereunder referred to as ''cartridge'') several ten times. Therefore, in Japan, many patients are using them for 10 years because they are easy to use and convenient to carry with, compared with the conventional disposable syringes.

Vial preparation is sealed with a rubber stopper so that the medical liquid can be used partially for several occasions. However, coring is reported to occur because rubber pieces are shaved off form rubber stoppers if an injector needle of 18 gauge (hereunder referred to as ''G'') is used.[1,2] Therefore, Japanese pharmaceutical firms have provided information to prevent coring in vials containing transfusion liquid and to give warning to the users. We made the coring occurrence test using cartridges because we considered it necessary to confirm if coring occurs in the cartridges, and if the rubber piece generated could pass through a needle. As a result, we found that coring occurred with extremely high frequency and that rubber pieces could pass through the needle.[3]

In this test, we checked if the same result could be obtained in the cartridges actually used by patients.

MATERIALS AND METHODS

We explained the objectives of this test and obtained consent from 30 patients hospitalized at Ohta-Nishinouchi Hospital (hereunder referred to as ''this hospital'') and collected the actually used Penfill® 300 (manufactured by Novo Nordisk Pharma, Co., Ltd.) as samples. Then, we set the cartridges to NovoPen® 300 (Novo Nordisk Pharma) and, using Micro-Fine Plus® 31 gauge 8 mm needle (Nippon Becton Dickinson, Co., Ltd.), we collected sample A: the primary injection (trial injection, 2 units), sample B: the secondary injection (2 units) and sample C: the cartridge remaining preparation (cartridge remaining preparation) (Fig. 1). After the samples are filtered using 0.45 μm filter (Millipore filter Type: HA, Lot No.: H7SH24028), we observed the samples filtrated using a microscope (OLYMPUS SZ-RT), measured the shape, number of pieces and the size and analyzed by one-way ANOVA and Scheff's test.

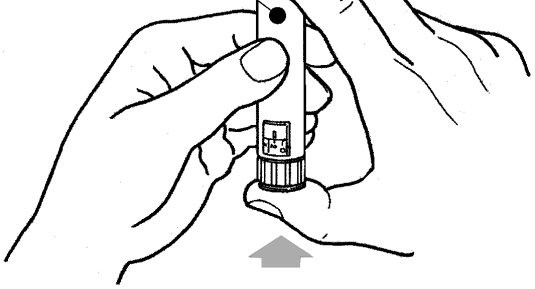

Fig. 1. Sampling Methods
Sample A: the primary injection (trial injection, 2 units), Sample B: the secondary injection (2 units) and Sample C: the cartridge remaining preparation (cartridge remaining preparation).

We selected the rubber pieces of 0.01 mm or larger in size and measured the longer diameter of aggregate rubber pieces and the length of needle-shaped or spiral-shaped rubber pieces. The test was conducted in November 1999. The cartridges were mounted on pen-type injectors and stored at room temperature (22—25℃), shielded from light, when they were used by the patients and when the observation was made. Each time the patients made self-injection, they replaced the needle with new one and wiped the rubber stopper with alcohol-sterilized cotton before the tip of the needle was inserted into the rubber stopper. The needle was inserted into the pen-type injector cartridge formulation in accordance with the ''Novo Pen® 300 Utilization Guide'' prepared by Novo Nordisk Pharma, Co., Ltd.

The average age of the 30 patients from whom the samples were collected was 59±18, HbA_{1c} was 8.0 ±1.6%, the number of injections made per day was 3 ±1, the unit of injection per day was 29±16 units, the number of insertion made to the collected cartridges was 26±15 and the amount of insulin collected was 0.9±0.4 ml.

RESULTS

1. Coring Occurrence Rate (Table 1) The coring occurrence rate of the 30 samples was 22 samples (73%) for Group sample A, 14 (47%) for Group sample B and 29 (97%) for Group sample C. Most of the rubber pieces in Group sample A and sample B were in aggregate shape while the rubber pieces in Group sample C are mostly in needle-like shape (Fig. 2). Spiral-shaped rubber pieces were found only in Group sample C.

2. Size of Rubber Pieces Many of the rubber pieces of Groups sample A and sample B were smaller than 0.01 mm in diameter, while the rubber pieces of Group sample C were relatively larger in diameter, 0.01 mm or more. When we compared the rubber pieces of 0.01 mm or more in diameter, we obtained the following results: the average size of Group sample A was 0.07±0.06 mm in diameter. The average size of Group sample B was 0.04±0.02 mm and the average size of Group sample C was 0.18± 0.15 mm in diameter (Fig. 3). The size of rubber pieces of Group sample C was significantly larger in diameter than those of Groups sample A and sample

occurrence rate'' gives insulin vial number. Except for these, gives rubber pieces number.

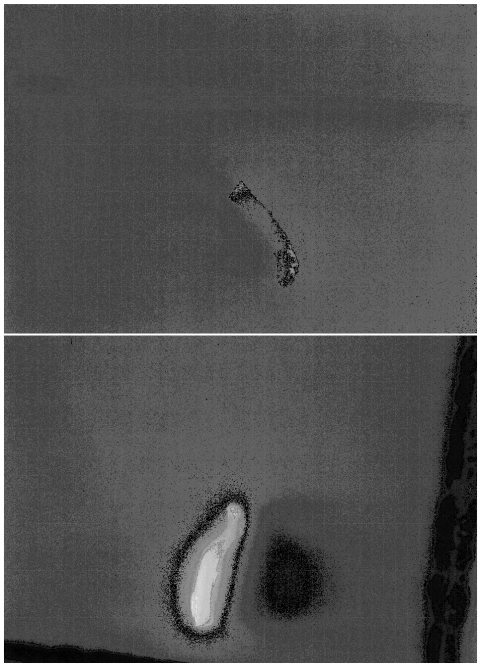

Fig. 2. Needle-Like Shape Rubber
(magnification×140)

B ($p<0.01$ by Scheff's test).

3. Observation of the Inside of Rubber Stopper

By observation of the inside of rubber stoppers, we found that the rubber pieces were pushed out by a series of needle insertion and depressions were made by the dropped rubber pieces (Fig. 4).

present, Japanese transfusion and medicine manufacturers are collaborating to issue brochures to prevent coring and to instruct users how to insert an injector needle. The brochures tell you to (i) insert a needle slowly and vertically, (ii) not to twist the needle while it is inserted and (iii) not to insert it at the same spot.

In Japan, insulin self-injection charge is not covered by the health insurance since 1981. Since then, with the advent of the pen-type injector and the extensive education to diabetes patients, it has become widely introduced for both type 1 and type 2 diabetes patients.

We investigated the occurrence of coring from insulin vial formulation for syringes (29G) and insulin cartridge formulation for pen-type injector (30G, 31G) at storage temperature (6—8℃/22—25℃), insertion angle (90°/60°) and the number of insertion (10/30 times). As a result, we have found that coring may occur when thin 29-31G needles for subcutaneous injection are used. Coring also occurs when vial formulation for syringes is stored at a cool place. Coring occurred for the cartridge formulation for pen-type injector in both cases.[3] Therefore, we conducted this test to check whether coring occurs in the cartridges which was used for actual self-injection by the patients. It was found that coring occurred at a very high ratio of 97% in the cartridges actually used by the patients.

From the pictures showing the inside of the rubber stopper, it is judged that the rubber pieces come out because the needle shaves off the rubber pieces when it is mounted on the pen-type injector. The material of rubber stoppers used for insulin formulation has dual layer structure consisting of butyl rubber and natural rubber.[4] The purpose of using the material is to prevent coring and to avoid any effect on the insulin. To minimize the shaving off of rubber pieces, the cutting face of the needle (inner needle)

sample A sample B sample C

Fig. 3. Size of Rubber Pieces of 0.01 mm or more in Diameter
Sample A: the primary injection (trial injection, 2 units), Sample B: the secondary injection (2 units) and Sample C: the cartridge remaining preparation (cartridge remaining preparation). Data are presented at means ± SD. *$p<0.01$ by Scheff's test.

Fig. 4. Inside of Rubber Stopper
(magnification × 44)

which is inserted into the rubber stopper of the cartridge is so designed that has no blade part. However, we observed no improvement in this test and coring occurred with high probability. To ''insert needles while rotating them on the same spot'' seems to be one of the greatest factors to cause coring, rather than the rubber material and the cutting face because a number of needle-shaped rubber pieces were found in the remaining insulin preparation.

Many small rubber pieces were found in Group sample A and Group sample B. The 31G needle has an outer diameter of approximately 0.26 mm and the inner diameter of approximately 0.15 mm.[5] As the diameter of a number of rubber pieces found in the sample A and sample B of this test is less than 0.15 mm and could pass through the needles, it is strongly suggested that these small rubber pieces may be injected into the subcutaneous tissue.

A ''trial injection'' to release 1 or 2 units of insulin preparation is performed to take out air after the needle is fixed before injection and to check if no fault with the injector has occurred. Then, the unit of insulin for injection (2 units in this case) is set and injected. At first, we expected that there would be very little chance for the rubber pieces to go through the needle. Even if some rubber pieces may have entered in the needle when the needle is inserted, they are discharged when a trial injection is made and there would be no rubber pieces in the actual injection. However, rubber pieces were also found in Group sample B in this test. Therefore, it is very a serious problem because many rubber pieces were found in Group sample B as well as in Group sample A, indicating a very high possibility that rubber pieces may be injected into the subcutaneous tissue.

A number of coring seems to have occurred because the needle mounted on Novo Pen® 300 which is used in this test is inserted by rotating it at the same spot. However, the pen-type injector currently available in the market employs the same inserting method. Therefore, we have to find out a way to prevent coring by enhancing the needle fixing method to the cartridge formulation in future.

In addition, as we found that rubber pieces were passed through an injector needle in this test, we have to pay attention to the possibility of ''foreign substance'' mixture. As the insulin self-injection is subcutaneous injection into the upper arm, abdominal

Mr. Masahiko Sato of Koriyama Plant of Novo Nordisk Pharma for cooperation for this test and measurement.

REFERENCES

1) Sakai T., Kho H., Mastuki A., *Jpn. J. Anesthesia*, **45**, 1533–1535 (1996).
2) Kubota H., Katahira M., Sumioka T., Wakiichi M., Taniyama E., Miyahara K., *ICU & CCU*, **21**, 743–745 (1996).
3) Asakura T., Seino H., Mizuno M., Nozaki S., Abe R., *Jpn. J. Hosp. Pharm.*, **25**, 407–413 (1999).
4) Internal document of Novo Nordisk Pharma, Co., Ltd.
5) Internal document of Nippon Becton Dickinson, Co., Ltd.
6) Akira A., *IRYO*, **51**, 201–204 (1997).
7) Leslie C. G. et al., *J. Allergy Clin. Immunol.*, **71**, 250–254 (1983).
8) Guntram S., *Diabetes Care*, **16**, 155–165

要旨

注射針を輸液剤等のゴム栓に穿刺するときに，ゴム栓からゴム片が削り取られるというコアリングが報告されている．実際に自己注射を行っている患者のインスリンバイアルでもコアリングが発生しているかを確認した．入院患者30名よりインスリンカートリッジを回収し，空打ち液，注入液，カートリッジ残液を試料とした．発生したゴム片を顕微鏡下で観察し形状と個数，大きさを測定した．コアリングの発生率は，空打ち液の発生率は73%，注入液は47%，カートリッジ残液は97% であった．形状は，針を通過している空打ち液と注入液では塊状が多く，針を通過していないカートリッジ残液では針状が多かった．空打ち液と注入液では小さなゴム片が多数確認されたことにより，ゴム片が皮下内に注入される可能性が強く示唆された．コアリングの原因としては，針を同一個所に回転させて刺すためと考えられる．そのため，今後はペン型注射器への針の装着について構造上の改良が必要である．コアリングは注射液の異物混入という点で，医学的にも薬学的にも非常に重大な問題である．今後はラテックスアレルギーやリポディストロフィーなどとの関連も検討する必要がある．