muscle fascias may be present. This can be better observed in an axial histologic cross-section (fig. 1) that evidently shows several layers surrounding the nerve fascicles, including an outer layer that cannot always be clearly separated from the adjacent epineurial layers. Both layers are very thin ($\leq$ 0.2 mm). Thus, by intentionally breaching this layer, we believe that both layers are punctured, and the needle tip is inside the nerve, which we referred to as intraepineurial.

However, to objectively verify this position, we adopted two additional parameters, that is, the position of the needle tip adjacent to the hypoechoic (black) round to oval-shaped nodules combined with distention of the nervous structure after small volume injection. For that reason, it might have been more appropriate to define "inside the nerve" as parafascicular (next to the nerve fascicles). The outside location was verified by indentation of a hyperechoic layer by pressure from the needle tip and by the absence of nearby black nodules. This could have been described as nonparafascicular. Thus, we are confident that our measurements really represent intraneural and extraneural needle tip placement. In fact, the accompanying figures of Morfey and Brull show the same configuration of black, round to oval-shaped nodules. Unfortunately, the position of their needle during injection is not shown. Furthermore, they suggest that if they accept our description and conclusions, they may have performed intraneural injections of the supraclavicular fossa much of the time. Actually, figure 2 in their study can be considered as a confirming sign that shows what has actually happened during their blocks, but what always was difficult to interpret: the presence of local anesthetic fluid adjacent to nerve fascicles. Because their retrospective survey[2] did not reveal long-term neurologic injury, it underlines our previous statement that intraneural injection does not invariably result in neurologic injury.[3,4]

The relative amount of connective tissue in combination with the thinness of epineurial and outer layers may further explain this phenomenon.[4] Our findings may be generalizable to nerves at other anatomic sites. Recently, Robards *et al.*[5] reported findings that are similar to those of ours for the popliteal sciatic nerve block. They observed intraneural injection in all cases with a motor response at a stimulation current of 0.2–0.4 mA. Therefore, our conclusion that stimulation thresholds more than 0.2 and less than or equal to 0.5 mA are not reliable to prevent intraneural needle tip position was verified at a second anatomical site.

In conclusion, a minimum stimulation threshold of less than or equal to 0.2 mA is reliable for parafascicular placement of the needle in ultrasound-guided supraclavicular block and possibly for other anatomic sites as well. Can this minimum current predict whether needle placement and local anesthetic injection will cause neurologic injury? No, it cannot. Are we convinced that our measurements inside and outside the nerve are reliable? Yes, we are convinced. Finally, are the ultrasound-guided supraclavicular blocks of Drs. Mofrey and Brull actually intraneural? Yes, that is our opinion, when anesthetic fluid is found adjacent to nerve fascicles.

We thank Drs. Mofrey and Brull for their interesting contribution to the continuing discussion on a possible relation between intraneural injection and neurologic injury.

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A Case of Accidental Hypotension Caused by Drug Leakage through the Rubber Piston in a Prefilled Inovan Injection 0.3% Syringe

To the Editor:

The use of prefilled syringes is recommended as a strategy to minimize errors in intravenous drug administration during anesthesia and intensive care.[1] Prefilled syringe formulations of potent cardiovascular drugs are available to provide rapid access for critically ill patients. The prefilled syringe that requires assembly is composed of two parts: A plastic syringe plunger and an airtight syringe barrel with a rubber piston at one end and the enclosed drug. The operator has to assemble the syringe by fitting the plunger to the piston at an appropriate position before fixing the syringe into the syringe pump. We encountered a rare case of accidental hypotension as a result of failed dopamine delivery caused by drug leakage from a Prefilled Inovan injection 0.3% syringe (marketed by Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan; manufactured by Terumo Corp., Tokyo, Japan). This leakage was noticed approximately 4 h after the start of the syringe pump infusion and appeared to be caused by plunger/piston misassembly. We report this case briefly to draw special attention to hazardous misassembly that may occur when using a prefilled syringe requiring assembly.

The case involved an elderly patient admitted urgently to our hospital for the treatment of pneumonia and dehydration. To manage his hypotension of 60/42 mmHg, a dopa-

mine infusion at a rate of 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started using a prefilled dopamine syringe (prefilled Inovan injection 0.3% syringe) delivered *via* a syringe pump (Termo STC-523, Terumo Corp.). An attending nurse replaced a new prefilled syringe and restarted the syringe pump. However, the patient's blood pressure measured by palpation fell abruptly to 42 mmHg approximately 4 h after restarting the prefilled dopamine syringe. Another attending nurse noticed a large volume of air in the extension tube, the three-way stopcock, and the barrel of the dopamine syringe. She immediately removed all the air in these components, reset the dopamine syringe into the syringe pump, and restarted it. After the patient's blood pressure was restored to 88/50 mmHg, the nurse exchanged the whole infusion system with new equipment. The volumes of drug and air in the dopamine syringe were 13 ml and 26 ml, respectively. We could not calculate the precise volume of air that had already been injected into the patient through the intravenous line, and fortunately the patient had no detectable injury as a result of this incident. Biomedical equipment technicians checked this syringe, the extension tube, the three-way stopcock, and the syringe pump carefully, but did not find any defect in these devices. We could not locate the source of the problem.

We sent the relevant syringe-infusion line assembly to the manufacturer for detailed inspection to identify the source of drug leakage and air influx, which appeared to occur at the piston that was fitted to the syringe barrel. We asked the manufacturer about the test results of the plunger/piston assembly that has been approved as medical equipment. The engineers responded as follows: They put the prefilled syringe in question to the liquid leakage test for syringe piston under compression in accordance with the International Organization for Standardization 7886–1: 1993–10-01.[2] There was no leakage in the rubber piston. Airtightness was maintained in the syringe, the extension tube, and the three-way stopcock. Next they examined situations that might produce drug leakage and how the leakage occurred during use of the prefilled syringe. The examination revealed the following: When the operator pushed the plunger into the rubber piston without turning it, there were some cases where the male screw thread molded at the top end of the plunger could not engage entirely the female screw thread molded on the inside wall of the rubber piston. Under this condition, the cylindrical rubber wall of the piston gradually became partially contorted as pressure was applied to the plunger after continuous infusion was started. This situation led to dislodging of the rubber piston, leaving a gap between the outside wall of the rubber piston and the inside wall of the barrel, and resulting in drug leakage as air entered through the gap (fig. 1). Consequently, the plunger/piston misassembly was proven to be the cause of erratic drug delivery, resulting in the abrupt onset of hypotension. The manufacturer had received the same incidental reports from several hospitals regarding the drug leakage from prefilled Inovan injection 0.3% syringes. They already had knowledge of the problem; however, they could not promptly supply a newly designed syringe for preventing an incorrect plunger/piston assembly.

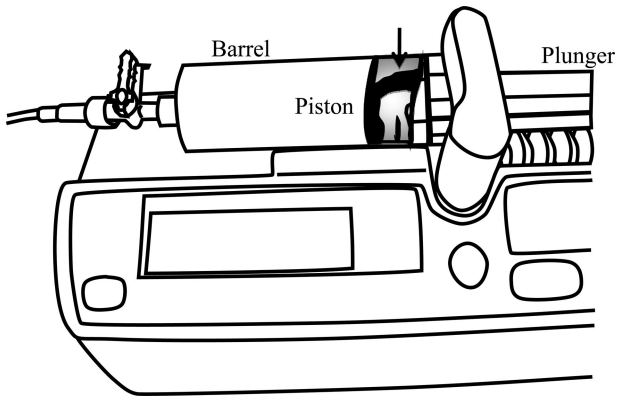

Fig. 1. Schematic representation of the situation in which a force applied to the plunger contorts the rubber piston when a prefilled syringe is used with a syringe pump. The gap (*arrow*) breaks the seal between the barrel of the syringe and the rubber piston, resulting in drug leakage as air entered through the gap. This plunger/piston misassembly caused an incident during drug administration.

Regarding the piston/plunger assembly of syringes for use with power-driven syringe pumps, International Organization for Standardization 7886–1 and 2 only describe the following requirements: The components of the syringe should be designed in such a manner that it is not possible easily to withdraw the plunger completely from the barrel, and the fit of the piston on the plunger should be such that relative axial movement between the two is kept to a minimum to reduce the possibility of siphoning. However, these International Organization for Standardization standards were not originally intended for syringes prefilled with an injection formulation by the manufacturer or syringes supplied with the injection formulation as a kit for filling by a pharmacist.[2,3] The designs for the piston/plunger assembly depend entirely on manufacturers.

The cause of the present error in intravenous drug administration was probably attributable to the design of the piston/plunger assembly that varies between manufacturers. However, we have no precise information about their designs. We selected four different commercially available prefilled syringes and compared the configurations of their plunger/piston assemblies. In the case of the Inovan 0.3% injection syringe, only the uppermost part of the plunger head was molded with a small number of male threads, and the cylindrical wall of the rubber piston is thin. Under these conditions, the syringe is highly susceptible to contortion of the rubber piston during use and formation of a gap between the piston and the barrel. In contrast, in the cases of the Iopamiron Injection 300 syringe (iopamidol; marketed and manufactured by Bayer Healthcare, Bayer Schering Pharma, Osaka, Japan) and Nitrol injection for continuous infusion 25-mg syringe (isosorbide dinitrate; marketed by Eisai Co., Ltd., Tokyo, Japan; manufactured by Nipro Pharma Corp., Osaka, Japan), a deep portion of the plunger head is molded with male threads and the inside wall of the piston fits closely with the plunger head, leaving a narrow gap between the two.

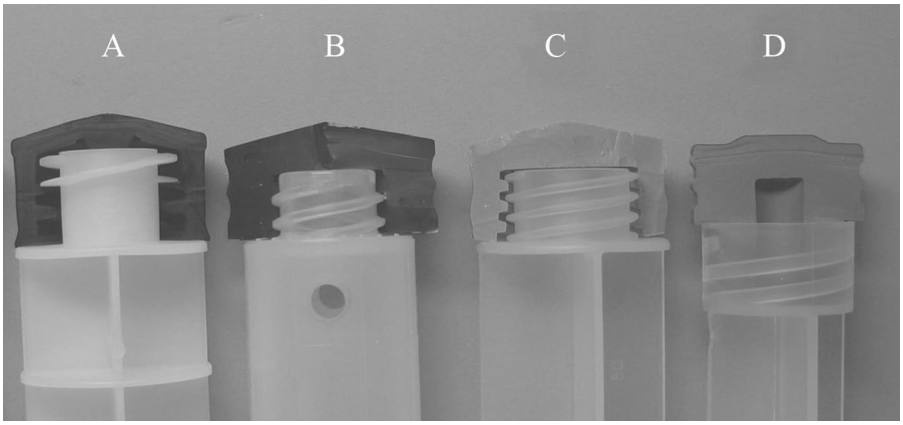

Fig. 2. The design of the plunger/piston assemblies in four prefilled syringes. The plunger head fits into the rubber piston that is sagittally sectioned. (*A*) Prefilled Inovan 0.3% injection syringe (Terumo Corp., Tokyo, Japan). (*B*) Iopamiron Injection 300 syringe (Bayer Healthcare, Bayer Schering Pharma, Osaka, Japan). (*C*) Nitrol injection for continuous infusion 25-mg syringe (Nipro Pharma Corporation, Osaka, Japan). (*D*) 1% Diprivan injection kit (AstraZeneca United Kingdom, Alderley Park, United Kingdom).

In the case of the 1% Diprivan injection kit (propofol; manufactured by AstraZeneca United Kingdom, Alderley Park, United Kingdom, imported and marketed by AstraZeneca K.K. Pharmaceuticals, Osaka, Japan), the piston has the thickest rubber wall among the four products and contortion hardly occurs, and the male screw threads of the piston engage with the female screw threads molded on the top portion of the plunger (fig. 2). A piston with a thick rubber wall is less likely to contort during use. However, the engineers of Kyowa Hakko Kirin and Terumo indicate that the thick wall may affect internal syringe compliance, influence the force needed to operate the plunger *via* a syringe pump, and may be associated with irregular drug delivery.[4]

We recommended that manufacturers provide a preassembled prefilled syringe with an integrated plunger/piston unit. However, the engineers indicated the following drawbacks of a preassembled prefilled syringe with an integrated plunger/piston: 1) Pressure may be exerted on the plunger during a fall or transportation of the syringe; 2) when the top film is peeled only partially during removal of the syringe, the finger grip may be caught by the film, resulting in tilting of the plunger with respect to the axial line of the barrel, which may cause plunger/piston misassembly; 3) the length of the whole unit becomes longer, posing problems in storage, transportation, and handling; 4) the manufacturers should apply to the Ministry of Health, Labor, and Welfare for changing a part of the original design, and approval will take more than 1 yr; and 5) the syringe pump structure may have to be modified to accommodate the newly arranged syringes. Based on these issues, Kyowa Hakko Kirin and Terumo are issuing appropriate warnings that the operator should not push the plunger into the rubber piston but should instead turn the plunger to engage the screw threads during assembly. They are also planning to modify the fundamental configuration of the plunger/piston assembly. We strongly recommend that the International Organization for Standardization, marketing companies, and manufacturers work together to supply prefilled syringes, particularly syringes with an integrated plunger/piston, that are safe and carefully designed to prevent plunger/piston misassembly by the operator.

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In Reply:

AstraZeneca would like to comment on the correspondence from Dr. Amagasa.

As pointed out in the article, the cause of the original failure is effectively down to poor assembly of the Prefilled INOVAN syringe. A key way to avoid this issue is for the users to always refer to the assembly instructions provided by the manufacturer. AstraZeneca provides clear and easy to follow assembly instructions on the 1% Diprivan Prefilled syringe exterior carton and interior tear-off lid on assembling the plunger rod to the rubber piston before use.

AstraZeneca also points out that the design of the thick wall impacting on the operation of the 1% Diprivan Prefilled