qualified persons in installation qualification, operational qualification, and standard operating procedure protocols.

Consequently, the solutions have to be prepared from high-purity batches, have to be kept in closed vials, and have to be refrigerated or stored at −20°C for a limited time only. If not, the sterility of the Millipore water and the saline solutions is not guaranteed, the composition of the acetone/HCl mixtures will change because of the low boiling points of the compounds, and the acetone in acidic media will undergo an aldol addition reaction forming 4-methyl-3-penten-2-on. We appreciate the effort of Petrik et al. to "finally" identify this well-known product, confirming the standard education of chemistry students (*6*).

If it was the intention of the present letter to the editor to reflect the relevancy of creating and following standard operating procedures for the synthesis of radiopharmaceuticals, we completely agree. Regarding the nontoxic compound 4-methyl-3-penten-2-on, Petrik et al. correctly state that its formation is negligible if acetone/HCl mixtures are stored with protection from light at −20°C or if freshly prepared mixtures are used.

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Side Effects Profile in Humans of ^{11}C-(+)-PHNO, a Dopamine $D_{2/3}$ Agonist Ligand for PET

TO THE EDITOR: ^{11}C-(+)-4-propyl-9-hydroxynaphthoxazine ((+)-PHNO) is a new PET ligand developed by our group. Binding assays show that (+)-PHNO displays high affinity and selectivity for the D_2 receptor (*1*). Recently, it has been noted that ^{11}C-(+)-PHNO has a preferential affinity and selectivity in vivo for the D_3 receptors (*2*). Because ^{11}C-(+)-PHNO is an agonist radiotracer for D_2 and D_3, it is likely to produce pharmacologic effects, in contrast to antagonist radiotracers. We reviewed all ^{11}C-(+)-PHNO consecutive scans obtained in our PET center for side effects. Mass injected (μg), subjects' weight (kg), and dose (μg/kg) were included in the analysis. Side effects were recorded on the basis of the subjects' self-report either during or right after finalization of the scan. A physician was available at all times to confirm and treat any possible side effects. Side effects were coded as 0 (no effect), 1 (nausea), or 2 (vomiting), based on our early experience with ^{11}C-(+)-PHNO (*3*). Odds ratios (ORs) were calculated using logistic regression analyses to investigate the relationship between dose, mass, and effects.

The number of reviewed ^{11}C-(+)-PHNO scans totalled 486. Injected mass ranged from 0.85 to 5.56 μg, with a mean of 2.30 μg (SE, 0.024 μg). Injected doses ranged from 0.01 to 0.08 μg/kg, with a mean of 0.03 μg/kg (SE, 0.0004 μg/kg). No effect was present in 84.6% of the scans reviewed; nausea was present in 14.3%, and vomiting in 1.1%. Symptoms arose 3–5 min after the injection and subsided within 7–12 min in all cases. In none of the cases was any medical action required.

In a logistic regression model including all subjects, nausea was significantly predicted by dose (Wald = 21.70, $P < 0.001$, OR 1.99) and mass (Wald = 16.319, $P < 0.001$, OR = 2.826), and vomiting was significantly predicted by dose (Wald = 7.31, $P < 0.007$, OR = 2.66) but not by mass injected (Wald = 0.694, $P = 0.405$, OR = 1.810). When only drug-free volunteers were analyzed ($n = 209$), no effect was present in 79.8% of the cases, nausea was present in 18.7%, and vomiting in 1.5%. In a logistic regression model including only drug-free volunteers, nausea was significantly predicted by dose (Wald = 6.98, $P < 0.008$, OR 1.54) and mass (Wald = 11.981, $P = 0.001$, OR = 2.843). Vomiting was predicted at a trend level by dose (Wald = 3.33, $P < 0.06$, OR 2) but not by mass (Wald = 0.105, $P = 0.746$, OR = 1.303). When only antipsychotic-treated participants were analyzed ($n = 66$), no effect was present in 97% of the cases, nausea was present in 3%, and no vomiting was present in any. In a logistic regression model including only these subjects, nausea was significantly predicted neither by dose (Wald = 2.25, $P < 0.13$) nor by mass (Wald = 0.000, $P = 0.99$). In all cases, when an injected dose of 0.029 μg/kg or less was selected, there was no relationship between dose and nausea.

The side effects reported in this study are consistent with the expected agonism at the D_2- and D_3-receptor (*4–7*).

We conclude that doses of ^{11}C-(+)-PHNO of 0.029 μg/kg or less are highly unlikely to produce any side effects in humans and that ^{11}C-(+)-PHNO is a safe agonist radiotracer for PET in human studies of health and disease.

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The Twilight Saga of Insulin Administration in Hyperglycemic Patients Undergoing ^{18}F-FDG PET

TO THE EDITOR: Roy et al. recently published a study adopting a standardized protocol of intravenous insulin administration to reduce glycemia in diabetic cancer patients undergoing ^{18}F-FDG PET (*1*). The authors claimed that the pretest intravenous insulin injection in diabetic patients is a realistic approach. However, several issues deserve further exploration before this standardized insulin protocol can be incorporated into daily PET practice.

In clinical tumor imaging, hyperglycemia has a recognized adverse effect on the quality of ^{18}F-FDG PET images because of competitive inhibition of ^{18}F-FDG uptake by glucose. Although insulin can be used as a glycemia-reducing agent, arbitrary prescription of insulin before ^{18}F-FDG injection may exacerbate muscular ^{18}F-FDG uptake and compromise tumor uptake, thus curtailing image interpretability (*2*). According to the study results of Roy et al., ^{18}F-FDG PET image quality was barely adequate in 75% of patients receiving insulin. This means every 1 of 4 scans must be repeated. Repeating a study is not a cost-benefit if the PET center does not have its own on-site cyclotron. Rescheduling is inconvenient to the patients and bothersome to the center staff. The set point to prescribe insulin in the study protocol of Roy et al. might account for their poor image quality. The Society of Nuclear Medicine recommends rescheduling the examination if the patient's blood glucose level is greater than 8.3–11.1 mmol/L (150–200 mg/dL) (*3*). The European Association of Nuclear Medicine also advises that an ^{18}F-FDG PET study should not be performed when the blood glucose level exceeds 11.1 mmol/L (*4*). If cancelling an examination or rescheduling an appointment is not feasible, we suggest the use of intravenous insulin at a blood glucose level of more than 11.1 mmol/L, instead of the 10.0 mmol/L stated by Roy et al. Additionally, we encourage hyperglycemic patients to have a temperate walk after insulin injection to reduce muscular uptake. In this way, the proportion of images of adequate quality would improve.

In their study, less favorable image quality was found with more glycemic reduction after insulin administration, and no significant correlation was observed between muscular uptake and parameters such as initial glycemia, total insulin dose, and number of insulin doses. Hence, the extent of glycemic reduction is not predictable and the chance of study failure is unavoidable. The implication is that we cannot select which hyperglycemic patient is suitable for insulin use. We also cannot apply the correct insulin dose to manage glycemic reduction before imaging. These phenomena can be explained by nonuniform insulin sensitivity among hyperglycemic patients. Therefore, Roy's standardized insulin protocol, an illogical practice such as sliding-scale insulin (*5*), is a problematic recipe for glycemic control in hyperglycemic patients undergoing ^{18}F-FDG PET studies. Sliding-scale insulin is also associated with poorer glycemic control, a harmful roller-coaster effect between hyperglycemic and hypoglycemic episodes, and increased risks of hypoglycemia, as occurred in 6 patients (9.5%) in the study of Roy et al. Thus, their standardized insulin protocol might be a risky strategy.

To obtain a useful diagnostic image of ^{18}F-FDG PET, one should ensure that the patient has fasted overnight and has a blood glucose level of less than 8.3 mmol/L in the early morning on the day of the PET scan. A good method is to do a "practice run" by checking the patient's blood glucose levels for at least 3 d before the ^{18}F-FDG PET appointment (*6*). If the morning blood glucose level is persistently higher than 8.3 mmol/L, the scheduler needs to recognize this problem well before the scan appointment and request that the diabetologist manage the glycemic status by basal and nutritional insulin therapy with a supplemental insulin regimen (*7*). To avert the possibility of irreversibly unreadable images, hypoglycemia, and transcellular-shift hypokalemia, before establishing specific guidelines for using insulin in hyperglycemic patients undergoing ^{18}F-FDG PET we should have the patients fast and we should not administer additional insulin.

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