Direct Healthcare Professional Communication

Date: 01Sep2022

Dexmedetomidine (Precedex™): Increased risk of 90-day mortality in intensive care unit (ICU) patients ≤65 years.

Dear Healthcare professional,

Pfizer in agreement with the Saudi Food and Drug Authority (SFDA), would like to inform you about risk of 90-day mortality in intensive care unit (ICU) in patients ≤65 years associated with use of Dexmedetomidine.

Summary

- In 3904 ventilated critically ill adult intensive care unit (ICU) patients, the SPICE III trial Quantify potential heterogeneity of treatment effect (HTE), of early sedation with dexmedetomidine (DEX) compared with usual care, and identify patients who have a high probability of lower or higher 90-day mortality according to age, and other identified clusters.

- When compared to other sedatives, dexmedetomidine was linked to a higher risk of 90-day mortality in patients ≤65 years (odds ratio 1.26; 95% credibility interval 1.02 to 1.56).

- The effect of age on mortality was most noticeable in patients hospitalized for reasons other than post-operative care, and it increased as APACHE II scores increased, and age decreased. The mechanism is unknown, and the significance of the difference could not be determined.

- These findings should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in younger patients.

- The product information of dexmedetomidine containing products will be updated with a warning statement describing the evidence, and risk factors, for increased risk of mortality in critically ill ICU patients ≤65 years of age.

Background on the safety concern:

Dexmedetomidine containing products are indicated for:

- Is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Precedex should be administered by continuous infusion not to exceed 24 hours.

- Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Precedex prior to extubation.

- Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

The academia-sponsored SPICE III trial enrolled about 4000 ICU patients needing mechanical ventilation, who were randomly allocated to receive sedation with either dexmedetomidine as primary sedative or with standard of care (propofol, midazolam, or other sedatives). Although the target sedation range was light sedation (RASS -2 to +1), deeper sedation levels (RASS -4 and - 5) were also allowed. The administration of dexmedetomidine was continued as clinically required for up to 28 days after randomization.[1]

Altogether, 3904 patients were included in an intention-to-treat analysis. Results are shown in Table 1 below. The study showed no difference in 90-day mortality overall between the dexmedetomidine and the usual care group (propofol, midazolam, or other sedatives). The median age of patients included in the analysis was 63.7 years.[1]

In subsequent analyses, a heterogeneity of treatment effect of dexmedetomidine has been identified:[2] an increased risk of 90-day mortality (odds ratio 1.26 [95% CrI 1.02-1.56]) was observed among patients ≤ 65 years of age. While the mechanism is yet unclear, the heterogeneity of effect on mortality from age was most prominent in patients admitted for other reasons than post-operative care, and increased with increasing APACHE II scores and with decreasing age. Table 1: Death from any cause at 90 days: primary outcome Dexmedetomidine n/total (%) Usual care n/total (%) Total 566/1948 (29.1) 569/1956 (29.1) Subgroup per age ≤ median age 63.7 years 219/976 (22.4) 176/975 (18.1) > median age 63.7 years 347/972 (35.7) 393/981 (40.1)

The product information of dexmedetomidine containing products will be updated with a warning statement describing increased risk of mortality in ICU patients ≤65 years of age.

Table 1: Death from any cause at 90 days: primary outcome

	Dexmedetomidine n/total (%)	Usual care n/total (%)
Total	566/1948 (29.1)	569/1956 (29.1)
Subgroup per age		
≤ median age 63.7 years	219/976 (22.4)	176/975 (18.1)
> median age 63.7 years	347/972 (35.7)	393/981 (40.1)

Call for reporting for adverse reactions:
Reporting suspected adverse reactions is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

- **Saudi Food and Drug Authority National Pharmacovigilance Center:**

Unified Contact Center: 19999
Toll Free Number: 80024900000
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

- **Pharmacovigilance Department in the company:**
  E-mail: SAU.AEReporting@pfizer.com

Company contacts point:
For more information, please contact Pfizer Medical Information:
MedInfoMEandAfrica@pfizer.com

References
1. SHEHABI, Yahya, et al. Early sedation with dexmedetomidine in critically ill patients. New England Journal of Medicine, 2019, 380.26: 2506-2517. 2. SHEHABI, Yahya, et al. Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. Intensive care medicine, 2021, 47.4: 455-466.

This Direct Healthcare Professional Communication has been approved by the Saudi Food and Drug Authority (SFDA).

Sincerely

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