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Dexmedetomidine: Increased risk of mortality in intensive care unit (ICU) patients ≤65 years

Dear Healthcare professional,

The Marketing Authorisation Holders (MAHs) for dexmedetomidine-containing products in agreement with the European Medicines Agency and the Agenzia Italiana del Farmaco (AIFA) would like to inform you of the following:

Summary

- **The SPICE III study was a randomised clinical trial comparing the effect of sedation with dexmedetomidine on all-cause mortality with the effect of "usual standard of care" in 3904 ventilated critically ill adult intensive care unit (ICU) patients.**

- **Dexmedetomidine was associated with an increased risk of mortality in the age group ≤65 years compared with alternative sedatives (odds ratio 1.26; 95% credibility interval 1.02 to 1.56).**

- **This heterogeneity of effect on mortality from age was most prominent in patients admitted for reasons other than post-operative care, and increased with increasing APACHE II scores and with decreasing age. The mechanism is not known.**

- **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 is being updated with a warning statement describing the evidence, and risk factors, for increased risk of mortality in ICU patients ≤65 years of age.**

Background on the safety concern

Dexmedetomidine containing products are indicated for:

- sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).
- sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

The academia-sponsored SPICE III trial enrolled 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). 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). 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: 90-days mortality

	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 is being updated with a warning statement describing increased risk of mortality in ICU patients ≤65 years of age.

Call for reporting

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 : https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

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.

AIFA takes the opportunity to remind all Healthcare Professionals of the importance of reporting suspected adverse drug reactions, as an indispensable tool to confirm a favorable benefit/risk ratio in the real conditions of use.
Reports of Suspected Adverse Reaction from drugs should be sent to the Pharmacovigilance Manager of the Structure to which the Operator belongs.
This Direct Healthcare Professional Communication is also published on the AIFA website (http://www.agenziafarmaco.gov.it) and it's consultation is recommended for the best professional information and citizen service.