A multinational, drug utilisation study to investigate the use of dexmedetomidine (dexdor®) in clinical practice in the EU

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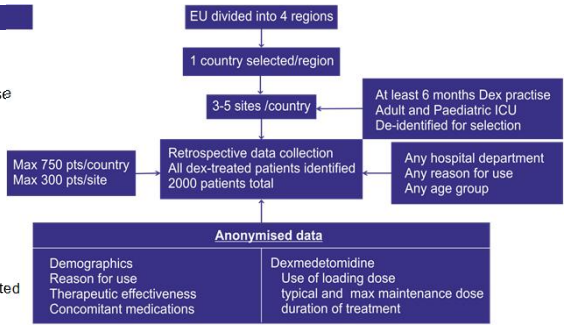
Background

- Dexmedetomidine is an α-2 adrenoceptor agonist for intravenous sedation approved in the US as Precedex® for ICU sedation in 1999 and for procedural sedation in 2007.
- Approved in the European Union (EU) in September 2011, as Dexdor®, for sedation of adult ICU patients.
- The EU licence specifies that Dexdor should be used in an ICU environment, without a loading dose, within dose range 0.2 – 1.4 µg/kg/h and is not recommended for children.
- The global medical literature on dexmedetomidine describes applications in many different clinical situations and populations, including children, involving numerous administration routes.
- The Committee for Medicinal Products for Human Use of the European Medicines Agency requested this study to explore possible off-label use of Dexdor in clinical practice in the EU, especially in children.

Methods

- Multinational, non-interventional, retrospective chart review in Finland, Poland, Germany and Austria.
- Institutions had established and frequent dexmedetomidine use based on Dexdor® sales.
- Study oversight and final site selection by independent multi specialist Steering Group.
- Ethics committee approval was obtained and the study notified to local authorities whenever required by local regulations. All patient data were anonymised at time of entry, allowing patient informed consent to be waived.
- Patient data was recorded into an electronic case report form with automated data verification checks.
- Administrations restarted after a gap of >48 hours were collected separately but linked to the same patient.



Results

2000 patients received 2159 administrations of dexmedetomidine during the 18 months data collection period (13 June 2013 to 04 December 2014).

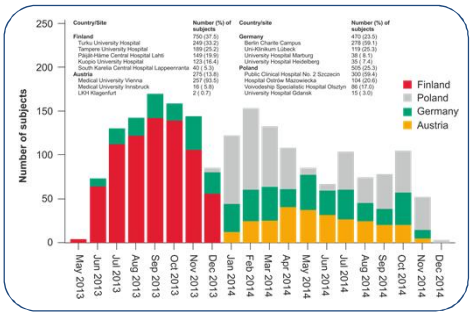


Figure 1. Administration of dexmedetomidine by month and by country

Demographic characteristics of all patients

	Finland N = 750	Poland N =505	Germany N = 470	Austria N = 275	Total N = 2000
Sex, n (%)					
Female	168 (22.4)	167 (33.1)	125 (26.6)	96 (34.9)	556 (27.8)
Male	582 (77.6)	338 (66.9)	345 (73.4)	179 (65.1)	1444 (72.2)
Age, median (range)	61 (0-102)	63 (15-92)	63 (15-93)	57 (0-88)	62 (0-102)
Age by category, n (%)					
≤ 27 days	3 (0.4)	-	-	2 (0.7)	5 (0.3)
>27 days to <2 years	14 (1.9)	-	-	11 (4.0)	25 (1.3)
2-11 years	25 (3.3)	-	-	11 (4.0)	36 (1.8)
12-17 years	40 (5.3)	3 (0.6)	1 (0.2)	8 (2.9)	52 (2.6)
18-65 years	375 (50.0)	307 (60.8)	260 (55.3)	154 (56.0)	1096 (54.8)
>65 years	293 (39.1)	195 (38.6)	209 (44.5)	89 (32.4)	786 (39.3)

- There were 13 university hospitals and 3 general hospitals.
- No sites were possible from Southern Europe. Austria added as highest per-capita user of dexmedetomidine.
- The most common primary indication was ICU sedation (91-98%) in all countries except Poland (32.4%), where perioperative sedation (56.0%) was the most common primary indication.
- Of ICU sedation administrations, the most common reasons specified were agitation despite existing sedatives (28.9%), delirium (26.1%) and difficult to wean (15.2%).
- In 11/16 sites more than 95% administrations were in the adult ICU.
- 7/16 sites treated children with dexmedetomidine.

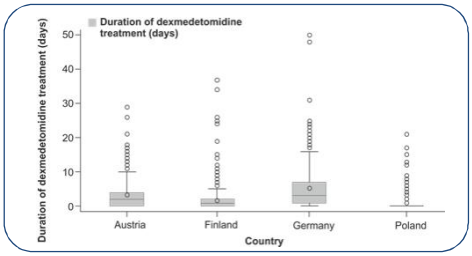


Figure 2. Duration of dexmedetomidine treatment

Abstract

Background: Dexmedetomidine (Dex) is a sedative drug approved as dexdor® for ICU sedation in adults in the European Union in 2011. This observational, retrospective drug utilisation study was requested by the Committee for Human Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to investigate Dex use in clinical practice.

Objectives: The objective of the study was to evaluate how Dex is used in the EU, with particular focus on offlabel use including the paediatric population.

Methods: Study countries and sites were chosen from those with highest dexdor use, based on sales. Site selection (blind) was conducted by a multinational, multispecialist, independent group. All patients treated with Dex at the study sites during the enrolment period were to be included. Anonymised data on demographics, treatment indication, Dex dosing, concomitant medications and treatment effectiveness were collected retrospectively from the patient records. Informed consent was waived to avoid influence of the study on the prescribing of Dex. Recruitment was limited to 750 patients per country or 300 patients per study site and was completed within 18 months of the first site initiation.

Results: Data from 2000 patients were collected from 16 hospitals in 4 EU countries (Finland 750, Poland 505, Germany 470, Austria 275) between 13th June 2013 and 4th December 2014. The median age was 62 years, with more males (70.2%) than females. The overall proportion of paediatric patients was 5.2% with the highest incidence in Austria and Finland. Dex was primarily used in adult ICU (86.0%) for ICU sedation (78.6%) and mostly dosed according the product label. Overall in 84.9% of administrations the intended sedative effect were obtained.

Conclusions: This drug utilisation study indicates that dexmedetomidine (dexdor®) is mostly used according to the terms of its product licence in the EU, although a variable degree of use was also seen in other settings and populations.

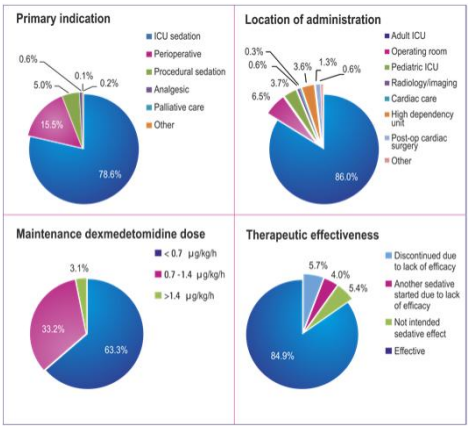
Conflict of interest statement: The study was funded by Orion Corporation Orion Pharma, Espoo Finland. MW, PP and CG were employees of Orion Pharma during the study. SPG is an employee of RTI International, a nonprofit research institute conducting research funded by public, private and commercial organizations, including pharmaceutical companies. RA has been a paid consultant for Orion Corporation (Espoo, Finland) and Abbott Laboratories (Abbott Park, IL, USA), the original codevelopers of dexmedetomidine, and also for Hospira (Lake Forest, IL, USA). He is also one of the three original patent holders of "Use of dexmedetomidine for sedative effect in patients in an intensive care unit" (WO/1999/049854). GC has received speaker fees from Orion Pharma and the Catholic University of Rome received research support for another study from Orion Pharma. ML is Director of EPES Epidemiology GmbH, a company working on issues of epidemiology and pharmacoepidemiology for various companies. NM declares no other relevant conflict of interest. SPG, RA, GC, ML and NM or their institutions received compensation from Orion Pharma for participation in the Scientific Steering Committee for this study

Acknowledgement: Prof. Corinne de Vries for input to strategy and study design as initial Chair of Steering Group

Dexmedetomidine was given almost always (98%) without a loading dose and always intravenously. The most common maintenance dose was <0.7 µg/kg/h (63%) and 9.3% patients received a dose >1.4 µg/kg/h for some period of their treatment, of which 4 (0.2%) occurred outside an ICU environment.

Median treatment duration was 1 day, although 2.6% patients continued >14 days

Results in complete population (2159 administrations)



Therapeutic effectiveness: based on both direct and indirect evidence in the patient record. A hierarchical derivation was structured in the order: 1. discontinued due to lack of efficacy, 2. another sedative started due to lack of efficacy, 3.not intended sedative effect. Remaining patients were classified "effective".

98.6% of administrations were given in the ICU environment. ICU sedation was the most common indication at all except 2 hospitals in 1 country where dexmedetomidine was given primarily for perioperative use (83.4%) or procedural sedation (53.8%).

84.9% of administrations produced the intended therapeutic effect. Dexmedetomidine was discontinued due to lack of efficacy in 5.7% and another sedative was started due to lack of efficacy in a further 4.0% of administrations. In 5.4% of administrations, dexmedetomidine was judged not to provide the intended effect.

Summary of dexmedetomidine use that deviated from the SmPC recommendations

No.(%) of administrations N = 2159	
Any deviation from the SmPC recommendation	790 (36.6)
Other than ICU sedation	463 (21.4)
Perioperative	335 (15.5)
Procedural sedation	108 (5.0)
Analgesic	14 (0.6)
Palliative care	2 (0.1)
Saving of sedatives and vasoconstrictors	1 (0.0)
Hypertension/tachycardia	1 (0.0)
Other	2 (0.1)
Outside ICU	223 (10.3)
Operating room	141 (6.5)
Radiology/imaging	14 (0.6)
Cardiac care/cardiology	6 (0.3)
Other	117 (5.4)
Other than ICU sedation and outside ICU	142 (6.6)
Maximum dose > 1.4 µg/kg/h	200 (9.3)
Paediatric use	125 (5.8)

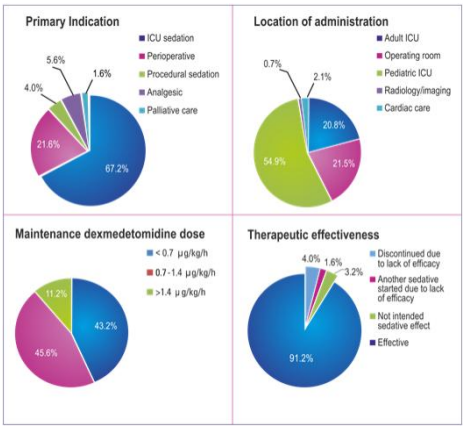
SmPC = Summary of Product Characteristics

In total, 790 (36.6%) administrations were given for a use that deviated in some way (indication, dose, location of use or age group) from the SmPC recommendations. The most common alternative use was perioperative.

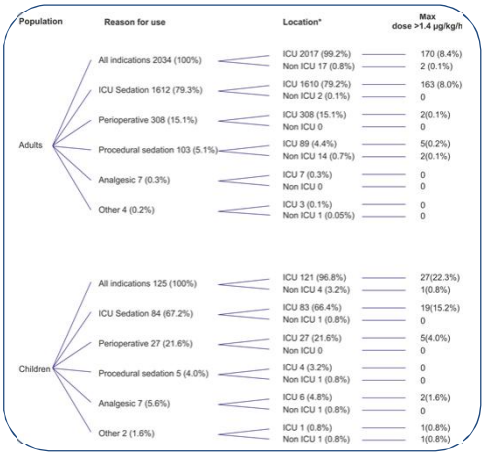
Paediatric use accounted for 125 (5.8%) administrations , almost all in Finland and Austria. All but 4 of these exposures occurred in an ICU environment.

Children were more likely than adults to receive a dose >1.4 µg/kg/h (28/125) although only one case was outside an ICU environment. Clearance of dexmedetomidine in young children has been shown to be higher than adults [1,2]

Results in children (125 administrations)



Most paediatric administrations (n=84) were for ICU sedation, followed by perioperative use (n=27). Uses other than ICU sedation were normally conducted with an appropriate level of patient monitoring and with the recommended adult dose range.



*"ICU environment", combining locations where the level of patient monitoring and care could be considered comparable to that in the ICU including paediatric ICU, operating room, post-operative anaesthesia care and coronary care units. Endoscopy, radiology and other such locations were considered to have uncertain levels of care and so not considered an ICU environment.

References

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Conclusions

This drug utilisation study of dexmedetomidine performed early after introduction of the product found that most patients were treated according to the SmPC, although there were important differences between countries and sites. Use in children was limited but significant and followed a similar pattern to that in adults. Administrations not fully according to the SmPC normally occurred in an ICU environment, under intense monitoring and reflected the clinical uses of dexmedetomidine most anticipated from the clinical literature.