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Intranasal dexmedetomidine in elderly subjects with or without beta blockade: a randomised double-blind single-ascending-dose cohort study

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Abstract

Background: The aim of this double-blind, placebo-controlled, single-ascending-dose study was to determine the safety and tolerability of intranasal dexmedetomidine in the elderly.
Methods: We randomly assigned 48 surgical patients ≥65 yr of age to receive single intranasal doses of dexmedetomidine or placebo (5:1 ratio) in four sequential dose cohorts: 0.5, 1.0, 1.5, and 2.0 μg kg^{-1}. Each dose cohort comprised two groups of six subjects: a group of subjects using β-blockers and a group not taking β-blockers. Vital signs and sedation depth (Modified Observer's Assessment of Alertness and Sedation [MOAA/S] and bispectral index) were measured for 2 h after administration. Blood samples were taken to determine dexmedetomidine plasma concentrations.
Results: One subject (1.0 μg kg^{-1}) had acute hypotension requiring ephedrine. Systolic arterial BP decreased >30% in 15 of 40 subjects (37.5%) receiving dexmedetomidine, lasting longer than 5 min in 11 subjects (27.5%). The MAP decreased >30% (>5 min) in 10%, 20%, 50%, and 30% of subjects receiving dexmedetomidine 0.5, 1.0, 1.5, and 2.0 μg kg^{-1}, respectively, irrespective of β-blocker use. HR decreased 10–26%. MOAA/S score ≤3 occurred in 18 (45%) subjects; eight (20%) subjects receiving dexmedetomidine showed no signs of sedation. T_{max} was 70 min. C_{max} was between 0.15 ng ml^{-1} (0.5 μg kg^{-1}) and 0.46 ng ml^{-1} (2.0 μg kg^{-1}).
Conclusions: Intranasal dexmedetomidine in elderly subjects had a sedative effect, but caused a high incidence of profound and sustained hypotension irrespective of β-blocker use. The technique is unsuitable for routine clinical use.
Clinical trial registration: NTR5513 (The Netherlands Trial Registry 5513).

Keywords: beta-blockade; complication; dexmedetomidine; elderly; hypotension; intranasal; safety; sedation

Editor's key points

- Intranasal dexmedetomidine might provide a less invasive route of administration for sedation of elderly patients, but it has not been studied in this population.
- A randomised double-blind study analysed the sedative and haemodynamic effects of intranasal dexmedetomidine in healthy elderly surgical patients.
- Intranasal dexmedetomidine had a sedative effect, but caused a high incidence of profound and sustained hypotension irrespective of β-blocker use.
- The technique is therefore not suitable for routine sedation in elderly patients.

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Intranasal administration of dexmedetomidine has been found to be safe and efficacious for the sedation of healthy adults and children.[1–4] Intranasal sedative administration has several benefits, one of which is that there is no need for i.v. access to achieve anxiolysis, and therefore, this route can be used to provide a comfortable and well-tolerated method of sedation for children, phobic patients, or those who are unable to cooperate because of an impaired cognitive function.

As the population ages and the incidence of major neurocognitive disorder increases,[5] caregivers will increasingly be confronted with elderly, uncooperative patients. Amongst patients with major neurocognitive disorders, almost half of those in need of dental treatment are uncooperative and untreatable without anxiolysis or sedation.[6] For these patients, minimal or light sedation may be preferable to general anaesthesia and deep sedation as the latter two are risk factors for the development of postoperative cognitive decline and delirium.[7–9] When sedating vulnerable elderly patients, healthcare providers must take into account the possible effects of age-related physiological changes, such as decline of renal and hepatic function and change in body composition, which can alter pharmacokinetics in the elderly.[10]

No prior knowledge of the safety of intranasal dexmedetomidine in the elderly is available. Our hypothesis was that a single dose of intranasal dexmedetomidine can be administered to elderly people safely with respect to haemodynamic changes, irrespective of concurrent β-blocker use. We performed a double-blind placebo-controlled single-ascending-dose study to investigate the safety, tolerability, and the sedative properties of four intranasal doses of dexmedetomidine in elderly subjects. Many elderly patients take β-blockers, which might aggravate the cardiovascular effects of dexmedetomidine. We therefore included in each dose cohort equal numbers of patients taking β-blockers and patients not taking β-blockers.

Methods

Study management and registration

This study was performed at the University Medical Center Groningen, Groningen, The Netherlands, in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice and the applicable regulatory requirements. Approval of the responsible ethics committee was received (NL55716.042.15), and all subjects provided written informed consent. The study was registered in the Dutch Trial Register (NTR5513).

Study execution

This was a study with a double-blind placebo-controlled single-ascending-dose design. We studied four sequential doses of intranasally administered dexmedetomidine: 0.5, 1.0, 1.5, and 2.0 μg kg^{-1}. In young adults and children, dosages of 1.0 and 1.5 μg kg^{-1} have shown to be effective.[1–4] Given the fact that elderly adults might plausibly be more susceptible to these doses, the first cohort received a smaller dose of 0.5 μg kg^{-1}. For completeness, and in case the elderly were less susceptible, we included a larger dose of 2.0 μg kg^{-1}. Each dose cohort consisted of 12 subjects: six using β-blockers and six not using β-blockers. The subjects within each dose cohort were randomised in a 5:1 ratio to receive either dexmedetomidine or placebo (normal saline 0.9%). Randomisation was performed by the hospital pharmacy using an online randomisation programme (www.randomization.com, accessed on February 3, 2016). The anaesthetist, sedation practitioner, and subjects were blinded to both the randomisation and the study drugs. Dexmedetomidine was provided by the hospital pharmacy in ampoules in blinded packages. Dexmedetomidine (Dexdor®; Orion Corporation, Espoo, Finland) in 2 ml ampoules (100 μg ml^{-1}) was used for subjects randomised to the dexmedetomidine group. Normal saline 0.9% prepared in 2 ml blinded ampoules was used as placebo. The ampoules were drawn up into a 2 ml syringe by a nurse not involved in the study and labelled by this nurse with a coded blind-study label from the same package.

Eligible subjects were elderly patients undergoing surgery under general anaesthesia. Inclusion criteria were age ≥65 yr, BMI ≥17.5 and ≤30.5 kg m^{-2}, total body weight >50 kg at screening and check-in, ASA physical status 1 or 2, and a modified Mallampati score I or II. Exclusion criteria were contraindications to the use of dexmedetomidine[11]; history or presence of a significant disease (ASA physical status >2); significant cardiovascular disease risk factors; significant coronary artery disease or any known genetic predisposition to cardiac arrhythmia (including long QT syndrome); psychiatric disease; history of any illness or medication use that might confound the results of the study or pose an additional risk to the patient by their participation in the study; surgery within the past 90 days before dosing judged to be clinically relevant febrile illness within 5 days before dosing; history or presence of alcoholism or drug abuse within the past 2 yr; hypersensitivity or idiosyncratic reaction to components of dexmedetomidine, placebo, or to compounds related to the study medications; single 12-lead ECG with QTcF interval >450 ms at screening, and patient refusal.

On the day of surgery, the subjects were transferred to a quiet room with low ambient light 2 h before the planned start time of their surgery. The subjects were monitored constantly during the entire study period. Emergency equipment and drugs were immediately available to treat hypotension, hypertension, or other symptoms of cardiovascular or ventilatory compromise. Monitoring of vital signs was started before the start of the study: 3-lead ECG, non-invasive BP measurements, and pulse oximetry were used to monitor vital signs. Additionally, a bispectral index (BIS) monitor (BIS VISTA™ monitor; Medtronic, Dublin, Ireland) was used, and end-tidal CO_2 was measured by combined oral–nasal capnography (Smart CapnoLine®; Oridion Medical Ltd., Jerusalem, Israel). Before dexmedetomidine administration, i.v. access was established and a baseline blood sample was collected from the i.v. cannula. Data from the vital signs monitor were automatically recorded in the digital patient Data Management System CS-EZIS-ChipSoft (ChipSoft Elektronisch Zorg Informatie Systeem; ChipSoft BV, Amsterdam, The Netherlands) at 15 s intervals. The subjects did not receive sedative or anxiolytic premedication. To avoid bias from BP elevation induced by preoperative anxiety, we compared BP on arrival with preoperatively measured BP; the lower of the two was used as baseline. We used the time-logged CS-EZIS system (ChipSoft BV) to record the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score and clinical events and findings relevant to the study. The subjects were treated by an anaesthetist or a registered sedation practitioner under indirect supervision of an anaesthetist.

Dexmedetomidine or placebo was administered intranasally via a MAD atomizer (LMA® MAD Nasal™ Intranasal

Table 1 Stopping criteria.

Group	Criteria
Haemodynamic	Hypotension: Systolic, diastolic or mean arterial bloodpressure >30% below baseline with signs of hypoperfusion for more than 5 minutes or needing escape medication
	Hypertension (Systolic blood pressure > 180mmHg; diastolic blood pressure >110 mmHg) for more than 5 minutes
	Bradycardia (heart rate <40 bpm for more than 5 minutes with signs of circulatory inadequacy)
	QTcF change from baseline >100 ms or total QTcF of >500 msec
Respiratory	Oxygen saturation [SpO_2] <90% not resolved by simple verbal or light tactile stimulation
Sedative	Sustained MOAA/S score of $\leq$1 for $\geq$5 consecutive minutes.
Miscellaneous	Any clinically significant AEs that the Sponsor and PI consider a safety concern
	Any serious adverse events (SAEs) which are considered by the PI as related to study drug

Mucosal Atomization Device; Teleflex Medical, Westmeath, Ireland). The volume in the syringe was adjusted to obtain the correct dose, depending on the dose cohort the subject had been assigned to. Volumes larger than 1 ml were distributed evenly over both nares so as not to exceed the recommended maximum volume of 1 ml per nare. Previous studies have used volumes in excess of 1 ml per nare, but have divided these between both nostrils to minimise swallowing.[12,13] Subjects were lying in the bed in a semi-recumbent position (45° angle) with the head tilted backwards during administration, after which the subjects were asked to remain in bed and not to engage in activities or spontaneous speech except for responses required for MOAA/S scoring. ECG, SpO_2, end-tidal CO_2, and BIS monitoring were performed continuously. BP was measured at 2.5 min intervals for the first 45 min and at 5 min intervals thereafter. MOAA/S was scored at 5 min intervals. Venous blood samples were taken at baseline and 10, 15, 20, 30, 45, and 90 min after administration of the study drug, with 5 ml of blood drawn and discarded before sampling. Measurements were continued for a minimum of 90 min and a maximum of 120 min. Thereafter, patient care was handed over to the anaesthetic team responsible for anaesthesia during surgery, ending the study period.

A safety check was incorporated in the study design. The subjects were sequentially assigned to ascending dose cohorts. After each cohort was completed, a safety committee (CRMB, MMRFS, and ARA) met and applied *a priori* stopping criteria (Table 1) to determine if it was safe to proceed to the next dose. When two or more subjects in a dose cohort from either the group using β-blockers or the group not using β-blockers met the stopping criteria, inclusion would be terminated for that group.

Statistical analysis

The study design was similar to that of 'first-in-man'-type single-ascending-dose studies. The primary endpoints were number of subjects experiencing a >30% decrease in systolic,

Table 2 Subject characteristics of the study population.

	All	Dexmedetomidine	Placebo
Total number of subjects	48	40	8
Sex (male/female) (n/n (%))	25/23 (52%/48%)	22/18 (55%/45%)	3/13 (38%/62%)
Age (Mean (SD) [range])	71.0 (4.9) [65-83]	71.0 (5.0) [65-83]	71.1 (4.4) [65-78]
ASA physical status 1 (n(%))	6 (17.5%)	4 (10%)	2 (25%)
ASA physical status 2 (n (%))	42 (87.5%)	36 (90%)	6 (75%)
Weight (kg, mean, SD)	78.1 (12.2)	79.3 (12.2)	72.2 (10.4)
Height (cm, mean, SD)	171 (9)	172 (9)	168 (7)
BMI (mean, SD)	26.5 (3.0)	26.7 (2.8)	25.5 (3.3)
Subjects using antihypertensive medication other than β-blockers	27	23 (57.5%)	4 (50%)
β-blocker use: Mean dose ($mg.day^{-1}$ and range) [% of subjects (n)]			
Metoprolol	78.85 (25-200) [54.2 (13)]		
Bisoprolol	3.33 (2.5-7.5) [25 (6)]		
Nebivolol	5 (5) [8.3 (2)]		
Carvedilol	25 (25) [4.2 (1)]		
Propranolol	10 (10) [4.2 (1)]		
Sotalol	80 (80) [4.2 (1)]		

Table 3 Effects on blood pressure and heart rate of dexmedetomidine and placebo per dose cohort.

Dose cohort (μg kg^{-1})	0.5 (*n*=10)	1.0 (*n*=10)	1.5 (*n*=10)	2.0 (*n*=10)	Placebo (*n*=8)
Number of subjects experiencing: (per dose cohort)	*n* (BB/NB)	*n* (BB/NB)	*n* (BB/NB)	*n* (BB/NB)	0
MAP decrease >30%	1 (0/1)	5 (4/1)	6 (3/3)	7 (3/4)	0
- Lasting more than 5 min	1 (0/1)	2 (2/0)	5 (3/2)	3 (2/1)	0
- Requiring an intervention	0	1 (1/0)	1 (0/1)	1 (1/0)	0
Heart rate (max%decr; mean(SD)	16.2 (9.2)	21.7 (7.9)	24.9 (10.0)	16.9 (9.1)	12.9 (6.2)
Time to nadir (min)	62	64	60	64	23
SBP (max%decr; mean(SD))	19.1 (10.3)	27.9 (12.2)	28.3 (11.3)	33.1 (8.8)	9.3 (7.9)
MAP (max%decr; mean(SD))	19.8 (11.6)	28.0 (11.6)$^{\$}$	31.3 (11.5)$^{\$}$	34. 3 (6.4)$^{\$}$	11.5 (6.5)
Time to nadir MAP (min)	75	68	65	80	39
DBP (max%decr; mean(SD))	19.2 (12.3)	29.5 (10.1)	33.8 (13.4)	34.1 (5.1)	19.1 (12.3)

BB: *n* subjects taking β-blockers; NB: *n* subjects not taking β-blockers; max%decrease: maximum percentage decrease, cohort mean (SD); MAP: mean arterial pressure. $: significantly different from placebo; SBP: Systolic arterial blood pressure MAP: Mean arterial blood pressure; DBP: Diastolic arterial blood pressure.

diastolic, or mean arterial BP below baseline for more than 5 min; the number of subjects per dose cohort experiencing bradycardia (HR <40 beats min^{-1}) for more than 1 min; and the maximum change from baseline in HR.

The secondary endpoints were the maximum change from baseline in systolic, diastolic, or mean arterial BP in 2.5–5 min intervals per dose cohort; the time of peak plasma concentration of dexmedetomidine T_{max}; peak plasma concentration of dexmedetomidine C_{max}; mean change in sedation depth over time per dose cohort; and number of subjects per dose cohort reaching the stopping criteria.

There were no prior data available to inform a sample size calculation. We therefore pragmatically chose the sample size based on previous experience with similar studies of safety, efficacy, pharmacodynamics, and pharmacokinetics of other anaesthetic drugs. For the primary outcomes, simple descriptive statistics were used to summarise findings. Differences in proportions between groups were tested using the χ^2 test. We constructed a linear mixed model for the change of MAP over time. Initial factors in this model were age, sex, interaction between β-blocker usage and time, and interaction between use of other antihypertensive agents and time. Stepwise removal of non-significant factors (P>0.05) was used to construct the final model. In each step, the factor with the highest P-value was removed. In the final model, only factors with P-values <0.05 remained. Univariate analysis was used to investigate the effects of dexmedetomidine doses on HR and BIS. Statistical analyses were done in IBM SPSS Statistics, version 23.0.0.3 (IBM, Armonk, NY, USA).

Results

Between March 2016 and July 2017, 163 patients were eligible for inclusion based on a preliminary screening and the plan of their surgery, which had to allow for all study procedures to take place before the start of the surgery. Supplementary Figure S1 shows a Consolidated Standards of Reporting Trials diagram of the inclusion process and reasons for exclusion. The characteristics of included subjects and use of β-blockers in group BB are summarised in Table 2. No subjects dropped out of the study during the study execution. One subject's scheduled surgery was brought forward unexpectedly, which prevented us from taking the last blood sample at 90 min. The maximum recommended volume for intranasal administration (1 ml per nare) was not exceeded in any subject.

Of the 27 subjects using additional antihypertensive agents, there was no significant difference between dose groups and the placebo group in the proportions of subjects using diuretics (P=0.101), angiotensin-converting enzyme inhibitors (P=0.804), calcium channel blockers (P=0.923), or angiotensin II inhibitors (P=0.171). Furthermore, the proportion of subjects using additional antihypertensive medication did not differ between the group using β-blockers and the group not using β-blockers (P=0.56).

Subjects meeting the stopping criteria

One subject (in the 1.0 μg kg^{-1} dose cohort) met two of the defined stopping criteria. At 73 min after dexmedetomidine administration, he suddenly experienced symptomatic hypotension, bradycardia, severe nausea, and dizziness. This was managed with the administration of ephedrine (5 mg bolus i.v.), and a rapid 500 ml bolus of Ringer's lactate solution and nursing in Trendelenburg position. Thereafter, the bradycardia, hypotension, and complaints resolved quickly and did not return. No other stopping criteria were met by any of the subjects, and therefore, we continued including subjects into all dose cohorts.

Haemodynamic safety: hypotension, bradycardia, and hypertension

HR and BP tended to decrease over time. Table 3 presents the number of subjects with hypotension, hypotension lasting >5 min, and hypotension requiring an intervention, and the mean percentages decrease and time to nadir for systolic BP, MAP, and HR.

Hypotension

In this study, 37.5% (n=15) of subjects who received dexmedetomidine experienced a decrease in systolic BP of >30% from baseline, and in 27.5% (n=11) of subjects this lasted for >5 min. In addition, 47.5% of subjects (n=19) who received dexmedetomidine had a decrease in MAP of >30% from baseline, and in 27.5% (n=11) this lasted for >5 min (Table 3). None of these subjects (except for the subjects described previously) had

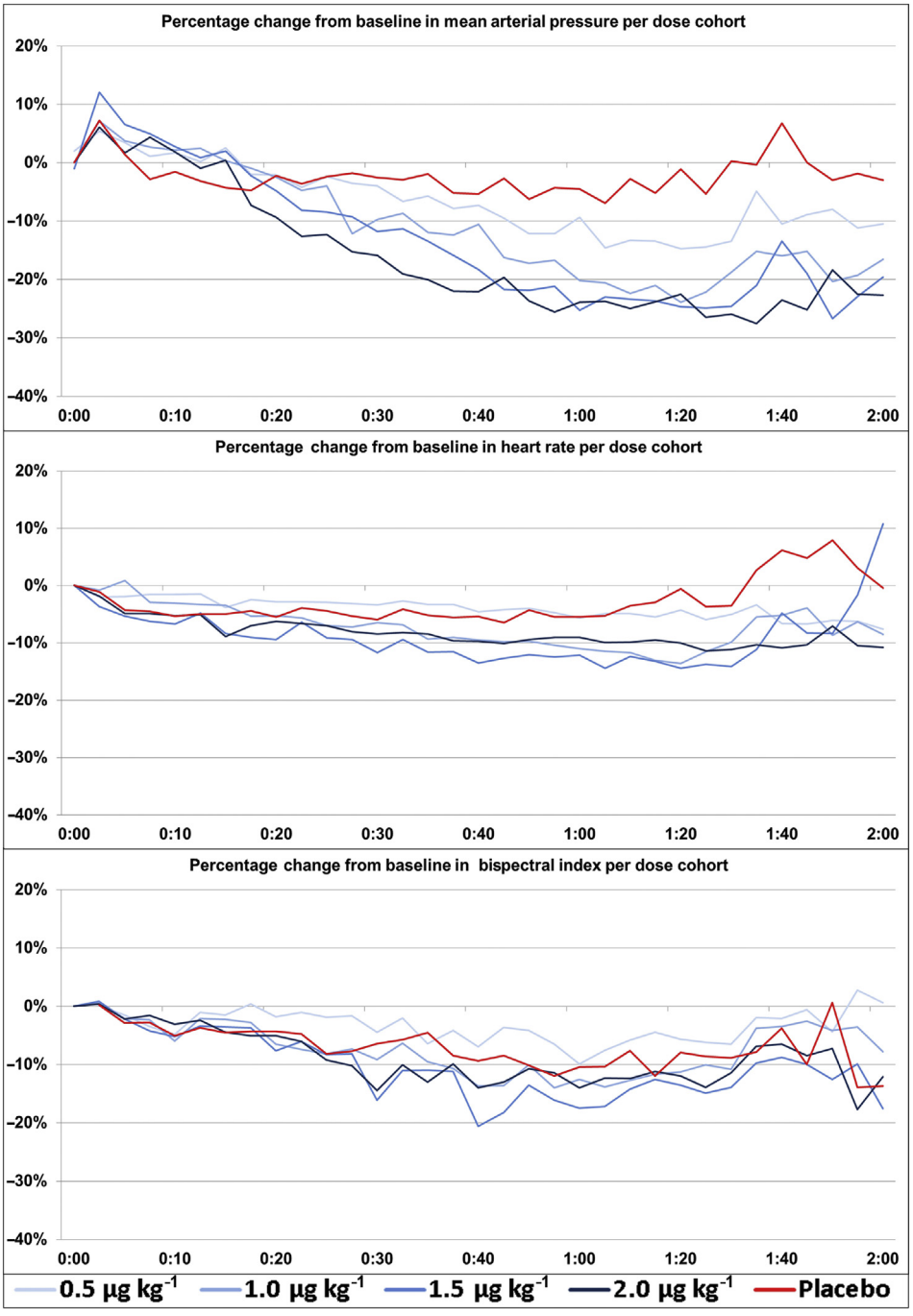

Fig 1. Percentage changes in mean arterial pressure, heart rate and bispectral index from baseline, per dose cohort.

clinical signs of hypoperfusion. No subjects in the placebo group had a decrease in BP of >30% from baseline.

A single 5 mg dose of ephedrine i.v. was administered to three subjects. This includes the aforementioned subject meeting the stopping criteria, and two additional subjects in whom ephedrine administration was deemed prudent because both had a history of cerebrovascular accidents and showed persistent declines in BP of >30% from baseline, although neither had complaints nor clinical signs of hypoperfusion, and therefore, did not meet the stopping criteria.

Bradycardia

Symptomatic bradycardia was observed in only one subject as described previously. No other subjects experienced bradycardia.

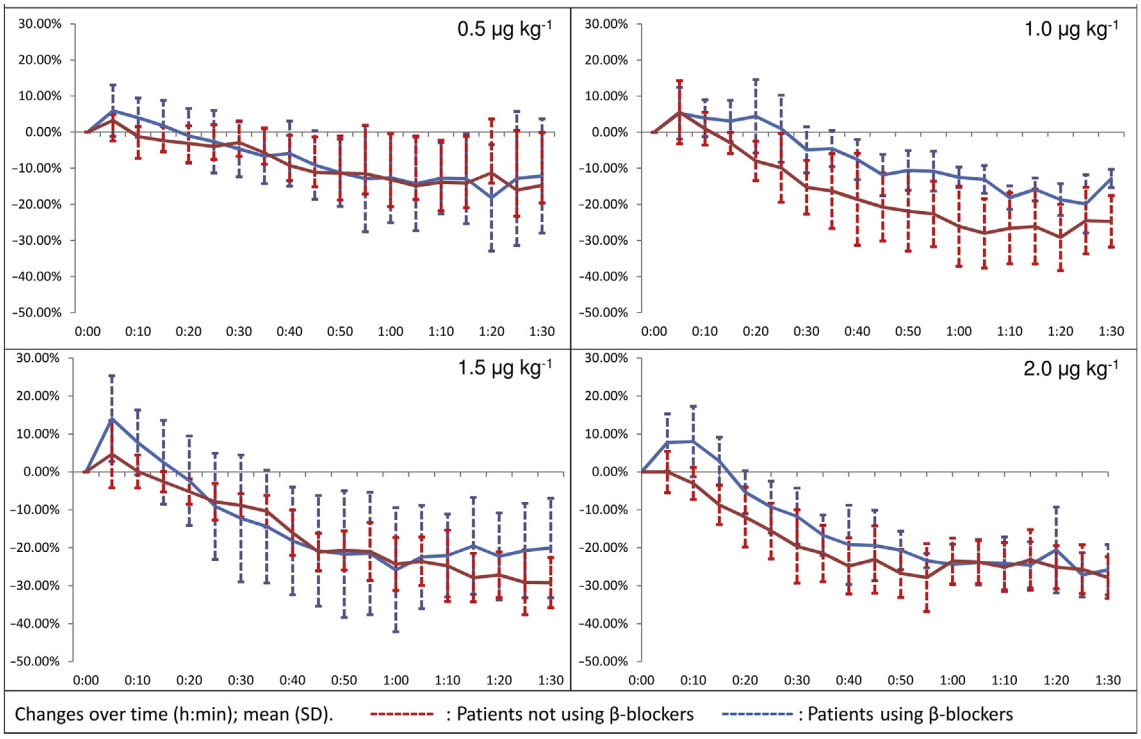

Fig 2. Percentage changes of MAP from baseline per dose cohort. SD, standard deviation.

Respiration

Respiration and arterial oxygen saturation remained relatively unaffected. Only one subject experienced SpO_2 <90% for >5 min, but this resolved after verbal stimulation. Four subjects displayed snoring with short decreases in SpO_2. These desaturations were benign and self-limiting.

Supplementary Figures S2–S6 plot the time course for all individual subjects for HR (Supplementary Fig. S2), systolic BP (Supplementary Fig. S3), MAP (Supplementary Fig. S4), diastolic BP (Supplementary Fig. S5), and pulse oximetry (Supplementary Fig. S6).

Secondary outcomes

The maximum percentage changes in systolic BP, MAP, and HR are summarised in Table 3. Figures 1 and 2 show the effects of dexmedetomidine dose over time on MAP, HR, and BIS. In the final linear mixed-effects model, only dexmedetomidine dose (F [5, 8.614]=63.906; P<0.001) was a significant factor in the decrease in MAP. Beta-blocker exposure, use of other antihypertensives, sex, and age were not significant factors. The mean difference in maximum MAP decrease between subjects receiving placebo and those receiving 0.5 μg kg^{-1} of dexmedetomidine was not significant. For higher doses, this difference was larger and significant ($P \leq 0.001$) (Table 2). Subjects who received dexmedetomidine also had a significantly larger decrease in HR (P=0.03) than those who received placebo with no significant effect from the use of β-blockers (P=0.89). The mean (standard deviation [SD]) time to the nadir of MAP of subjects in the dexmedetomidine groups was 73 (20) min (72 [18] min for group BB and 72 [20] min for group NB).

Sedative properties

All subjects were lucid (MOAA/S 5) and able to respond adequately to MOAA/S scoring at the start of the study period. BIS values could not be determined for four subjects because of technical failure. Subjects receiving dexmedetomidine were more sedated (as measured by BIS) than subjects receiving placebo (P=0.01). The mean (SD) time to the lowest BIS values was 65 (22) min (BB group: 65 [22]; NB group: 59 [45] min). One subject in the placebo group reached a MOAA/S score of 3; the BIS value at that time was 87. One subject (dose cohort 1.5 μg kg^{-1}) reached a BIS of 16 with a suppression ratio of 22, 35 min after dexmedetomidine administration. The MOAA/S score obtained 45 s later was 4 (BIS value was 37).

The lowest MOAA/S scores reached by subjects, the time to lowest BIS values and lowest MOAA/S scores, and the times to peak measured dexmedetomidine concentrations per cohort are summarised in Table 4. All subjects remained rousable at all times, although, when most sedated, six subjects required 'shake and shout' stimuli. The dose of dexmedetomidine correlated with the maximum decrease in BIS and the lowest MOAA/S score (Spearman's ρ: −0.43; P=0.003 and −0.633; P<0.001, respectively). Eight (20%) of the subjects in the dexmedetomidine groups did not display any clinical signs of sedation. Five of these subjects were in the lowest dose cohort of 0.5 μg kg^{-1}. The three other subjects were in dose cohorts BB15, NB10, and NB20, respectively. The minimum BIS values

Table 4 Sedative effects and pharmacokinetics.

	0.5	1.0	1.5	2.0	Placebo
	(*n*=10)	(*n*=10)	(*n*=10)	(*n*=10)	(*n*=8)
Cmax (ng ml^{-1})	0.15 (0.03)	0.26 (0.05)	0.42 (0.13)	0.46 (0.13)	0
Tmax: (min)	81	78	63	57	
max%-decrease BIS (mean (SD))	9.9 (9.9)	29.8 (10.9)	41.7 (17.8)	31.4 (13.4)	22.6(16.7)
Time to nadir BIS (min)	55	61	65	75	53
Lowest MOAA/S-score (number of subjects)					
5	5	1	1	1	5
4	4	7	2	1	2
3	1	2	6	3	1
2	0	0	1	5	0
1	0	0	0	0	0
0	0	0	0	0	0

C_{max}: maximal plasma concentration of dexmedetomidine; T_{max} time to highest plasma concentration of dexmedetomidine; BIS: BiSpectral Index; MOAA/S: Modified Observers' Assessment of Alertness and Sedation.

for these subjects ranged from 72 to 91. Supplementary Figure S7 plots the time course for all individual subjects for BIS.

Plasma dexmedetomidine concentrations

The peak plasma concentrations (C_{max}) per cohort are shown in Table 4. T_{max} (mean [SD]) was 70 (26) min. There was no significant difference in T_{max} between subjects taking β-blockers and subjects not taking β-blockers: 66 min (BB) and 71 min (NB) (P=0.39).

Tolerability

All subjects tolerated the administration of dexmedetomidine or placebo well: no subjects experienced discomfort from the intranasal administration. Three subjects complained of dry mouth, and three other subjects experienced mild nausea, but they did not vomit or require anti-emetics.

All subjects had uneventful procedures under general anaesthesia after participation.

Discussion

In this study of the safety and sedative properties of intranasal dexmedetomidine in elderly subjects, we found that, whilst the three highest doses had sedative properties, they caused a significant decrease in BP in a large proportion of subjects. Although only one subject experienced clinical signs of hypoperfusion, the degree to which systolic BP and MAP were affected in a high percentage of elderly subjects is a matter of concern. Furthermore, it was deemed prudent by the anaesthesiologist to administer ephedrine to two other subjects because the prolonged decline in BP was thought to present a risk.

We studied the use of intranasal dexmedetomidine with the intention to assess its safety and suitability for use in procedural sedation of the growing group of vulnerable elderly patients. Previous studies have shown that dexmedetomidine appears safe when used in younger adults. The dosages used in the current study were within the range that had been shown to produce minimal-to-moderate sedation in adults without causing significant hypotension.[1,2,14,15] The incidence of hypotension in the current study is notably different, however, from the results of previous studies of the effects of intranasal dexmedetomidine in younger adults.[1,2,14,15] In the study by Zhang and colleagues,[2] the maximum mean decrease in systolic BP was 9.0%, and Nooh and colleagues[1] reported no decrease of systolic BP of >20%. In the current study, dosages needed to induce minimal or moderate sedation (1.0–2.0 μg kg^{-1}) caused a change in systolic BP of >20% in all three dose cohorts and a decrease in MAP of >30% in a high percentage of subjects. Decreases in BP of the magnitude we found have been associated with an increased risk of perioperative stroke and renal and myocardial damage.[16,17]

In each dose cohort, we included equal numbers of subjects taking or not taking β-blockers. Elderly people frequently use β-blockers,[18] which could plausibly amplify the haemodynamic effects of dexmedetomidine. Our data do not support this, as the incidence of hypotension and bradycardia did not differ between subjects taking β-blockers or not, and the mean decreases in MAP and HR were not significantly determined by β-blocker use. In common with the general elderly population, a large proportion of subjects in our study were taking other antihypertensive medication at the time of the study. The proportions of subjects using additional antihypertensive medication did not differ significantly for subjects taking β-blockers or not. Further studies will be needed to determine whether other antihypertensive medications amplify the hypotensive effects of dexmedetomidine.

It took more than 60 min to reach the maximum sedative effect. This time may limit the usefulness of intranasal dexmedetomidine for procedural sedation. Although the time of onset of clinical effect and the time to maximum clinical effect in our study are comparable with those found in a study on younger adults, the maximum attained sedation depth was markedly different.[15] Only 45% of our subjects receiving dosages of 1.0 and 1.5 μg kg^{-1} attained a MOAAS score of 3 or lower, whereas in the study involving younger adults, 75% and 92% of the subjects attained a sedation level of MOAA/S $\leq$3 after the same respective doses.[15] Although the BIS and sedation scores in our study suggest a moderate level of sedation for procedural sedation in some subjects, we observed that the stimulation associated with MOAA/S scores brought almost all subjects back to a lucid state for a short period of time. This well-known property of dexmedetomidine

is probably the result of the fact that the sedative effect of dexmedetomidine primarily arises from actions on the natural sleep pathway.[19] The extent and duration of this arousal, accompanied by increases in BIS values, were recently quantified.[20] This does, however, give rise to doubts as to whether it will be useful for procedural sedation of patients without cognitive coping strategies, such as elderly patients suffering from major neurocognitive disorders who may need deeper, more sustained sedation. Yuen and colleagues[15] raised similar concerns about younger adults, stating 'whether these doses will produce clinical sedation in anxious patients facing surgery or other painful procedures will need to be evaluated'. Deeper sedation with dexmedetomidine will require higher doses, which will result in more profound haemodynamic effects.[20,21]

With regard to pharmacokinetic parameters, the results in our elderly population are comparable with those found in a study of intranasal dexmedetomidine in younger adults, in which a median C_{max} of 0.28 ng ml^{-1} after 1.0 μg kg^{-1} was found; for the same dose, we found a median C_{max} of 0.26 ng ml^{-1}.[22] In the current study, onset of the clinical effect of intranasal dexmedetomidine was at 20–30 min after administration. This is in accordance with findings from previous studies in younger adults.[1,22] Finally, T_{max} in the current study for 1.0 μg kg^{-1} is comparable with T_{max} found by Li and colleagues[22] (78 *vs* 75 min).

The current study has some noteworthy strengths and limitations. We performed a double-blind placebo-controlled study to minimise risk of bias. This is reflected by the differences observed between the dexmedetomidine group and the placebo group in the measurements of both haemodynamic parameters and observed sedation depth. The latter parameter was obtained using the MOAA/S score by a blinded observer, but also objectively by using the BIS monitor. In spite of the limited sample sizes, we were able to determine significant differences in effect size between dexmedetomidine and placebo for MAP and BIS with sufficient power (99% and 97%, respectively). The power for the test of the difference in maximum HR was lower (73%), owing to the limited sample size and effect size.

A limitation of our study is the fact that, with intranasal administration of any liquid drug formulation, a variable proportion of the administered volume can reach the pharynx and be swallowed, thus changing the drug absorption rate and possibly the maximum attainable plasma concentration. Swallowing of intranasally delivered drugs is dependent on many factors, one of which is the administered volume.[23] In the current study, the maximum recommended volume per nare of 1 ml[24] was not exceeded for any subject. We cannot rule out the possibility that an unknown quantity of dexmedetomidine was not absorbed by the nasal mucosa of some subjects, but was swallowed and thus delivered orally or absorbed by the pharyngeal mucosa. The bioavailability after oral administration of dexmedetomidine is only 16%,[25] whereas after intranasal administration it has been found to be 40.6% (95% confidence interval: 34.7–54.4%).[22] We administered a fixed concentration of dexmedetomidine so that different subjects received different volumes of drug, but have not controlled for the administered volume. These uncertainties prevent us from making more detailed comparative or predictive analyses of the pharmacokinetic profile and pharmacodynamic effects we found. If some of our subjects swallowed significant amounts of the administered dose, resulting in reduced bioavailability, this would have altered the time to peak effect, and would plausibly have underestimated the haemodynamic and sedative effects of the doses of dexmedetomidine in this age group. Additional studies that are able to control for volume, and preferably also for swallowing, are needed.

Data from the current study cannot be used to generate a full pharmacokinetic profile of dexmedetomidine after intranasal administration in the elderly. The subjects in this study received dexmedetomidine in the preoperative phase. As the subsequent induction of general anaesthesia would have influenced many important parameters determining the pharmacokinetic profile, we refrained from blood sampling at later stages, and therefore, limited ourselves to the pharmacokinetic measurements we have presented. The results do suggest, however, that the differences in haemodynamic and sedative effects found in our population and those in younger adults in previous studies are more likely to be attributable to pharmacodynamic than pharmacokinetic differences.

In summary, intranasal dexmedetomidine in elderly subjects had a sedative effect, but caused a high incidence of profound and sustained hypotension. The technique is therefore unsuitable for routine clinical use.

Authors' contributions

Study design: CRMB, MKD, ARA, MMRFS
Data collection: CRMB, MKD, ARA
Data analysis: CRMB
Data interpretation: CRMB, MKD, MMRFS, AV, ARA
Drafting of article: CRMB, ARA
Revision of article: all authors
Approval of the final version of the article and agreement to accountability: all authors

Declarations of interest

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Appendix A. Supplementary data

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