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Subcutaneously administered dexmedetomidine is efficiently absorbed and is associated with attenuated cardiovascular effects in healthy volunteers

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Abstract:	Purpose: Palliative care patients often need sedation to alleviate intractable anxiety, stress and pain. Dexmedetomidine is used for sedation of intensive care patients, but there is no prior information on its subcutaneous (SC) administration, a route that would be favored in palliative care. We compared the pharmacokinetics and cardiovascular, sympatholytic and sedative effects of SC and intravenously (IV) administered dexmedetomidine in healthy volunteers. Methods: An open two-period, cross-over design with balanced randomization was used. Ten male subjects received 1 µg/kg dexmedetomidine both IV and SC. Concentrations of dexmedetomidine and catecholamines in plasma were measured. Pharmacokinetic variables were calculated with non-compartmental methods. In addition, cardiovascular and sedative drug effects were monitored. Results: Peak concentrations of dexmedetomidine were observed 15 min after SC administration (median; range 15-240). The mean bioavailability of SC dexmedetomidine was 81 % (AUC0-∞ ratio x 100 %, range 49 - 97 %). The mean (SD) peak concentration of dexmedetomidine in plasma was 0.30 (0.10) ng/ml, and plasma levels associated with sedative effects (i.e > 0.20 ng/ml) for 4 hours after SC dosing. Plasma noradrenaline levels were significantly lower (P < 0.001) after IV than after SC administration. Subjective scores for vigilance and performance were significantly lower 0-60 min after IV than SC dosing (P < 0.001 for both). The onset of the cardiovascular, sympatholytic and sedative effects of dexmedetomidine were clearly less abrupt after SC than IV administration. Conclusions: Dexmedetomidine is relatively rapidly and efficiently absorbed after SC administration. Subcutaneous dexmedetomidine may be a feasible alternative in palliative sedation, and causes attenuated cardiovascular effects compared to IV administration.
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Suggested Reviewers:	Maud Weerink PhD Candidate in Anesthesiology, Rijksuniversiteit Groningen m.a.s.weerink@umcg.nl Recent review on pharmacokinetics of dexmedetomidine.

Subcutaneously administered dexmedetomidine is efficiently absorbed and is associated with attenuated cardiovascular effects in healthy volunteers

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ABSTRACT

Purpose: Palliative care patients often need sedation to alleviate intractable anxiety, stress and pain. Dexmedetomidine is used for sedation of intensive care patients, but there is no prior information on its subcutaneous (SC) administration, a route that would be favored in palliative care. We compared the pharmacokinetics and cardiovascular, sympatholytic and sedative effects of SC and intravenously (IV) administered dexmedetomidine in healthy volunteers.

Methods: An open two-period, cross-over design with balanced randomization was used. Ten male subjects received 1 µg/kg dexmedetomidine both IV and SC. Concentrations of dexmedetomidine and catecholamines in plasma were measured. Pharmacokinetic variables were calculated with non-compartmental methods. In addition, cardiovascular and sedative drug effects were monitored.

Results: Peak concentrations of dexmedetomidine were observed 15 min after SC administration (median; range 15-240). The mean bioavailability of SC dexmedetomidine was 81 % ($AUC_{0-\infty}$ ratio x 100 %, range 49 - 97 %). The mean (SD) peak concentration of dexmedetomidine in plasma was 0.30 (0.10) ng/ml, and plasma levels associated with sedative effects (i.e > 0.20 ng/ml) for 4 hours after SC dosing. Plasma noradrenaline levels were significantly lower ($P < 0.001$) after IV than after SC administration. Subjective scores for vigilance and performance were significantly lower 0-60 min after IV than SC dosing ($P < 0.001$ for both). The onset of the cardiovascular, sympatholytic and sedative effects of dexmedetomidine were clearly less abrupt after SC than IV administration.

Conclusions: Dexmedetomidine is relatively rapidly and efficiently absorbed after SC administration. Subcutaneous dexmedetomidine may be a feasible alternative in palliative sedation, and causes attenuated cardiovascular effects compared to IV administration.

Keywords: Dexmedetomidine, Subcutaneous, Pharmacokinetics, Palliative care

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INTRODUCTION

Patients in palliative end-of-life care often suffer from intractable anxiety, stress and pain, and may need pharmacological sedation. Such symptoms are commonly managed with opioids, benzodiazepines, antidepressants or antipsychotic drugs (1). As all of these agents have dose-related adverse effects, combinations are often used to decrease individual drug doses or for beneficial synergistic interactions. The use of opioids is associated with many adverse effects such as nausea, vomiting, constipation, and most importantly, respiratory depression (1-2). Benzodiazepines are efficacious sedatives but lack analgesic activity and may provoke delirium (3). Thus, there is a clinical need for alternative treatments to alleviate end-of-life symptoms.

α_2-Adrenoceptor agonists, in clinical use best exemplified by dexmedetomidine, are distinct in their mechanism of action from other clinically available analgesic and sedative agents (4-5). Dexmedetomidine has been demonstrated to induce dose-dependent sedation without major risk of ventilatory depression (6-8). Dexmedetomidine is also known to attenuate hemodynamic and endocrine stress responses (9-11).

Dexmedetomidine is in clinical use in more than 70 countries for sedation of adult intensive care unit (ICU) patients. In some countries, it also has regulatory approval for perioperative sedation (12). Based on its pharmacological mechanism of action and on several published case reports and uncontrolled studies, dexmedetomidine may provide benefits for patients in palliative care as it induces analgesia, sympatholysis and sleep-like sedation with relatively little risk of respiratory depression. Of note, dexmedetomidine-induced sedation is also associated with arousability, thus allowing the patient to communicate and remain in contact with family and caregivers (13-14). Confusion and delirium are seldom seen in ICU patients receiving dexmedetomidine, which contrasts with e.g. benzodiazepines and propofol (3, 15). Furthermore, dexmedetomidine has beneficial synergistic interactions with opioids and other sedative drugs. Dexmedetomidine is well

absorbed when administered intranasally (IN) (16), intramuscularly or buccally (17-19). However, there are no published reports on its pharmacokinetics after subcutaneous (SC) administration.

MATERIALS AND METHODS

Subjects and ethics

The study protocol (EudraCT 2015-004698-34, ClinicalTrials.gov identifier NCT02724098) conformed to the revised Declaration of Helsinki (20), and was approved by the Ethics Committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines. Written informed consent was obtained from eleven male subjects aged between 18 and 30 years. Their mean (SD) age and body mass index (BMI) were 22.6 (2.2) years and 23,9 (1,5) kg m^{-2}, respectively. Concomitant medications (except occasional paracetamol), current or recent significant illness, history of any kind of drug allergy or previous or present alcohol dependence, drug abuse, psychological or other emotional problems likely to invalidate informed consent or to limit the ability of the subject to comply with the protocol requirements were exclusion criteria.

Study design

The study was conducted according to a two-period cross-over design with balanced randomization. The study days were separated by three weeks. On the study days, subjects fasted from midnight until 5 h after drug administration. Water intake was allowed. Each study session was performed from 07:30 a.m. to 18:30 p.m. The subjects remained in a semi-recumbent position after cannulation until the end of the session, excluding bio-breaks (meals, toilet visits). Standard meals were served 5 and 9 h after dexmedetomidine administration.

The subjects were scheduled to receive 1 µg/kg doses of dexmedetomidine IV and SC in randomized order. IV doses of dexmedetomidine (Dexdor® 100 µg/ml, Orion Pharma, Espoo, Finland) were diluted in 0.9 % saline solution (Natriumklorid B. Braun® 9 mg/ml, B. Braun, Melsungen, Germany) and administered at a concentration of 8 µg/ml during 10 min by infusion (Perfusor® Space Infusion Pump, B. Braun). SC dexmedetomidine (Dexdor® 100 µg/ml) was

diluted in 0.9 % saline solution and administered at a concentration of 50 µg/ml during 10 min by infusion with the same pump.

Sampling

At the start of each study session, a venous catheter was inserted into a large forearm vein for safety reasons. An arterial catheter was inserted into a radial artery for blood sampling and blood pressure monitoring. Peripheral oxygen saturation was measured with pulse oximetry. Arterial blood samples (blood volume 5 ml) were collected immediately prior to administration of dexmedetomidine (baseline) and then at 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2 and 3 h after the start of the 10-min infusions into EDTA tubes for determination of concentrations of dexmedetomidine, adrenaline and noradrenaline in plasma. Further blood samples were collected at 4, 5, 6, 8 and 10 h for determination of dexmedetomidine. The samples were chilled in ice. Plasma was separated by centrifugation in a refrigerated centrifuge and samples were stored at –70 ^{o}C.

Dexmedetomidine and catecholamine analysis

Concentrations of dexmedetomidine in plasma were determined with a validated (21) reversed-phase high-performance liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS; Shimadzu Prominence HPLC connected to an AB Sciex API4000 mass spectrometer), with some modifications to a previously described procedure (22). Solid-phase extraction was performed with Sep-Pak® tC18 cartridges (Waters Corporation, Milford, MA, USA), and deuterium-labelled dexmedetomidine (from Toronto Research Chemicals, Toronto, ON, Canada) was used as the internal standard. The mobile phase was 0.1 % formic acid in a mixture of 1:1:1 (v/v/v) methanol/acetonitrile/water. The lower limit of quantitation (LLOQ) was 0.05 ng/ml. The within- and between-run precision of the assay (coefficient of variation) was within 5 % in the relevant concentration range. Concentrations of adrenaline and noradrenaline in plasma were measured using HPLC and coulometric electrochemical detection, basically as described previously

(23), but now adapted to a dedicated HPLC system provided by Thermo Fisher Scientific (Waltham, MA, USA). The analytical column was a reversed-phase C18 column (HR-80 C1), the detector was a Dionex Ultimate ECD-3000RS instrument coupled to a model 6011RS Ultra dual electrode, and the system was operated with Chromeleon v. 7 software (all from Thermo Fisher Scientific). The LLOQ for both catecholamines was 0.1 nM. The within- and between-run precision of the assay (coefficient of variation) was within 10 % in the relevant concentration range.

Pharmacokinetic analysis

Data were log-transformed before statistical analysis, but non-transformed results are reported. The peak plasma concentrations (C_{max}) and corresponding peak plasma concentration times (t_{max}) were observed directly from the data. For each subject, the terminal log-linear phase of the plasma dexmedetomidine concentration-time curve was identified visually, and the elimination rate constant (k_{el}) was determined by regression analysis on the basis of at least four time points. The elimination half-life ($t_{1/2}$) was then calculated from the equation $t_{1/2} = \ln 2 / k_{el}$. The area under the dexmedetomidine plasma concentration-time curve (AUC) was calculated using the trapezoidal method, with the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations. Apparent clearance (CL/F) and apparent volume of distribution of dexmedetomidine during the elimination phase (V_Z/F) were also calculated, with non-compartmental methods based on statistical moment theory. The pharmacokinetic analysis was carried out with WinNonlin software (version 4.1, Pharsight Corporation, Mountain View, CA, USA).

Pharmacodynamic measurements

Heart rate, intra-arterial blood pressure and peripheral oxygen saturation were recorded at times of blood sampling (immediately prior to administration of dexmedetomidine (baseline) and thereafter

at 5, 10, 15, 30 and 45 min and 1, 1.5, 2, 3, 5, 8 and 10 h after the start of dexmedetomidine administration). At the same time points, also psychomotor drug effects on vigilance and performance were assessed with visual analog scales (VAS). Subjective assessments (alert to drowsy, very good performance to very poor performance) were recorded with 100 mm horizontal VAS lines. For each pharmacodynamic variable, the AUC was determined using the trapezoidal rule.

Assessment of local tolerability

The local tolerability of SC and IV administered dexmedetomidine was assessed with VAS scores by the study participants and by visual inspection by the investigator immediately prior to drug administration (baseline) and at 1, 5, and 10 h. Subjective effects (no local pain/strong pain, no irritation/strong irritation, no pruritus/strong pruritus, no numbness/total numbness) were recorded. In the visual inspection by the investigator, possible local dermal irritation, inflammation, bleeding and swelling were recorded. For each assessment, the AUC was calculated using the trapezoidal rule.

Statistical analysis

In view of previous studies (16-17), we calculated that 8 subjects would be needed to detect a 30 % difference in the AUC of plasma dexmedetomidine at a power of 80 % and a level of significance of $P < 0.05$. To be prepared for drop-outs, we recruited 10 subjects. The primary outcome variables of this study were the observed concentrations of dexmedetomidine in plasma and its calculated pharmacokinetic parameters. The secondary variables were heart rate, blood pressure, plasma adrenaline and noradrenaline concentrations, sedative effects, and possible local adverse effects. The data were evaluated for normality of distributions with probit plots and the Shapiro–Wilk's W-test. Log-transformed data were analyzed but non-transformed results are reported. Differences in pharmacokinetic variables were analyzed using paired t tests. Pharmacodynamic data were analyzed

using analysis of variance (ANOVA) for repeated measurements. The results are expressed as mean values and SD, except for t_{max}, which is expressed as median (range). Explorative data analysis and statistical testing was performed using R language for Statistical Computing, version 3.3.2 (24), in RStudio, version 1.0.136 (25).

RESULTS

Ten male subjects (aged 19 to 27 y) were recruited, of whom eight completed the study. Eight subjects received both SC and IV dexmedetomidine and another two subjects received only SC dexmedetomidine. One subject missed his IV study session for personal reasons. Another subject was withdrawn from the study as a safety measure after the SC administration phase due to emergence of bradycardia of 32-39/min, at 1-5 h after drug administration; the bradycardia was not associated with subjective symptoms and resolved with no interventions. Calculations were based on 10 and 8 subjects during the SC and IV phases, respectively.

Instead of bolus dosing, we administered dexmedetomidine as 10-min infusions to avoid α_2-adrenoceptor-mediated vasoconstriction and hypertension that may ensue after rapid IV administration (26). Due to technical issues with infusion pumps, one participant received 1.07 µg/kg of dexmedetomidine during 11 min 42 s on both occasions and one participant received 0.78 µg/kg of SC dexmedetomidine during 7 min 47 s. All other dosages were 1 µg/kg and were given during 10 minutes. Drug concentration analysis resulted in 3 (2 %) and 8 (7 %) observed dexmedetomidine concentrations <LLOQ after IV and SC dosing, respectively. During the IV phase, 12 (12 %) of the noradrenaline concentrations were < LLOQ. For adrenaline, there were 38 (43 %) and 25 (23 %) measurements <LLOQ during the IV and SC phases, respectively. Concentration values < LLOQ were included in the calculations as equal to 50 % of the LLOQ, i.e. 0.025 ng/ml and 0.05 nM for dexmedetomidine and catecholamines, respectively.

Pharmacokinetic results

The calculated pharmacokinetic parameters are shown in Table 1 and mean (SD) plasma concentrations of dexmedetomidine are shown in Fig. 1. The mean (SD) peak concentration of dexmedetomidine in plasma was 0.30 (0.10) ng/ml after SC administration, and plasma levels previously associated with sedative effects (i.e. >0.20 ng/ml (6, 27) were maintained for 4 hours

after SC dosing. After IV administration, the mean C_{max} of dexmedetomidine was 2.42 ng/ml, observed at the end of the IV infusion. Peak concentrations of dexmedetomidine in plasma were observed 15 min after the end of the SC infusion (median; range 15-240 min). After 3 hours, similar plasma concentrations were measured during both study phases. The mean exposure ($AUC_{0-\infty}$) to dexmedetomidine was 36 % lower during the SC phase, but apparent mean $t_{½}$ was prolonged compared to the IV phase (1.9 h vs. 3.8 h, $P < 0.001$). The mean bioavailability of SC dexmedetomidine was 81 % (range 49 to 97 %).

Pharmacodynamics

There was a slight but statistically insignificant increase in mean arterial pressure (MAP) at the end of the IV infusion. Compared to the SC phase, mean MAP was significantly lower during 0-120 min ($P < 0.032$) after IV administration of dexmedetomidine (Fig. 2). Although heart rate decreased initially after IV dosing, there were no statistically significant differences between the treatments when maximum decreases or epochs over 0-30 or 0-60 min after drug administration were tested. Peripheral oxygen saturation remained unchanged during both phases in each subject.

Pronounced inhibition of sympathetic nervous system activity was reflected by reduced plasma noradrenaline concentrations after the IV administration of dexmedetomidine. The onset of this effect was less abrupt and the reductions were smaller after SC dexmedetomidine (Fig. 3). Plasma noradrenaline concentrations remained significantly smaller ($P < 0.001$) during the entire sampling period after IV administration compared to SC administration (Fig. 3). Similarly, noradrenaline AUC_{0-180} was significantly smaller ($P < 0.001$) during the IV phase. Plasma adrenaline concentrations were significantly lower for the first 60 min after drug administration during the IV phase ($P = 0.037$), but after that, there were no significant differences between the phases.

Subjective effects of dexmedetomidine are shown in Fig. 4. Scores for vigilance and performance were significantly lower at 0-60 min after IV than after SC dosing ($P < 0.001$ for both effects), but

at later time points, the subjects tended to be more sedated after SC than after IV administration. The performance scores were actually statistically significantly lower during the SC phase for the 60-600 min observation period (P = 0.023), but there was no significant difference in the vigilance scores during this period.

Local tolerability

There were no visible signs of local skin irritation at the infusion sites. No subjective local or systemic adverse events were reported.

DISCUSSION

We compared the pharmacokinetics of SC and IV administered dexmedetomidine with doses previously suggested for palliative sedation (28-29). We hypothesized that the bioavailability of SC dexmedetomidine would be sufficient for palliative dosing and that the hemodynamic side-effects of dexmedetomidine might be reduced by this route of administration because of slower entry of the drug into the systemic circulation compared to IV administration as a 10-min infusion. Our results show that the bioavailability of SC dexmedetomidine is sufficient for clinical utility, even if marked inter-individual variability was observed.

High peak concentrations in plasma were avoided by SC dosing, but after 3 hours, similar plasma concentrations were measured during both study phases. The exposure was 31% smaller during the SC phase during the sampling time ($AUC_{0\text{-}10\ h}$) compared to the IV phase. When based on $AUC_{0\text{-}\infty}$, the mean relative bioavailability of SC dexmedetomidine was 81 %. The pharmacokinetic parameters determined for IV dexmedetomidine were similar to those reported earlier (29).

In line with the pharmacokinetic results, the hemodynamic, sympatholytic and sedative effects of dexmedetomidine emerged significantly less abruptly after SC dosing when compared with IV administration. Previous studies have demonstrated that IV dexmedetomidine causes dose-dependent decreases in heart rate and blood pressure, with initial hypertension after larger doses, concomitantly with decreases in plasma catecholamines (6, 30-31). We wanted to diminish dexmedetomidine-induced bradycardia in the IV phase by administering 10-min constant-rate infusions, but IV dosing still resulted in significant decreases in heart rate and blood pressure. Compared to this, SC administration was associated with sustained and much smaller reductions, and may thus reduce the risk of hemodynamic depression compared with IV dosing.

One participant had asymptomatic bradycardia of 32-39/min from 60 to 300 min after SC administration of dexmedetomidine. He was an athlete with low resting heart rate of 40-42/min.

The results of previous studies indicate that dexmedetomidine causes significant cardiac conduction effects via depression of the sino-atrial node, thus decreasing resting heart rate by up to 15-20 % (7). We therefore excluded this subject from the IV part of the study, in order to avoid the risk of severe bradycardia. Apart from the observed hemodynamic changes, the subjects had no significant adverse effects. We did not record any changes in oxygen saturation. Similarly, with the hemodynamic effects, the onset of subjective sedation was delayed after SC dexmedetomidine compared to IV administration. Our results thus indicate that the sedative effects of SC dexmedetomidine may appear less abruptly and last longer compared to IV dosing. This could be beneficial when providing prolonged sedation for patients in palliative care, obviating the need for IV drug infusions. Our results thus suggest that SC dexmedetomidine might be an efficacious and safe addition to drugs used for palliative sedation. However, we investigated healthy volunteers, and no placebo control session was included in the study. Therefore, these findings should be considered as preliminary, and further studies are warranted.

Bioavailability of dexmedetomidine after intranasal, intramuscular, oral and buccal administration has been investigated previously (16-18). Our current findings suggest approximately similar bioavailability of dexmedetomidine after SC, IN and IM administration, and confirm that the bioavailability is sufficient for clinical usefulness also after SC administration. Further studies are, however, needed to warrant this administration route in clinical practice. Our study was conducted with a small number of healthy volunteer subjects. We collected plasma samples for the concentration measurements for 10 hours, which was reflected in the fraction of the extrapolated area (mean 28 %) in the area under the plasma concentration-time curve to infinity ($AUC_{0-\infty}$) during the SC phase.

Our study participants reported no subjective local adverse effects related to SC administration of dexmedetomidine. We could not see any local irritation of the skin around the SC dosing area.

However, in five subjects the area of drug administration felt slightly numb during the sampling phase, which is probably related to α_2-adrenoceptor mediated vasoconstriction caused by dexmedetomidine. These findings suggest that the SC route may be a safe mode to dose dexmedetomidine.

SC dexmedetomidine has been used in palliative care, but such use has only been described in some uncontrolled case reports (32-33). Dexmedetomidine has several beneficial pharmacological characteristics, it has a relatively short half-life, and it provides sedation that is associated with easy arousability. Furthermore, dexmedetomidine has opioid-sparing effects and it may reduce the likelihood of delirium, at least when compared to sedation with propofol or benzodiazepines. Further work is required to examine its possible role and utility in the management of terminal sedation in palliative care.

CONCLUSION

Dexmedetomidine is rapidly and efficiently absorbed after SC administration. Compared to IV administration, SC administration of dexmedetomidine may be a feasible alternative for patients requiring sedation.

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CONFLICT OF INTERESTS

M. Scheinin has been engaged in contract research for Orion Pharma, the manufacturer of dexmedetomidine. T. Saari has received honoraria for speaking at symposia organized by Orion Pharma. P. Uusalo has received speaker fee from Orion Pharma. The other authors declare that they have no conflicts of interest.

AUTHOR´S CONTRIBUTIONS

Panu Uusalo took care of the clinical phase of the study and data collection, participated in data analysis and statistical analysis and wrote the manuscript. Darin Al-Ramahi performed the analytical assays. Ida Tilli took care of the clinical phase of the study and data collection, participated in data analysis. Riku Aantaa designed the study, wrote the protocol, supervised and coordinated the clinical implementation of the study, and participated in data analysis. Mika Scheinin supervised the analytical assays, participated in data analysis and statistical analysis and wrote the manuscript.. Teijo Saari designed the study, analyzed the data, performed data and statistical analysis, and wrote the manuscript. All authors materially participated in the research and/or manuscript preparation. All authors have contributed to and approved the final manuscript.

FIGURE LEGENDS

Fig. 1 Mean (SD) dexmedetomidine concentrations in plasma after administration of 1 μg/kg of dexmedetomidine intravenously (closed circles) to eight or subcutaneously (open circles) to ten healthy volunteers. The concentrations are shown both on arithmetic and logarithmic scales (inset).

Fig. 2 Heart rate and mean blood pressure; mean (SD) after administration of 1 μg/kg of dexmedetomidine intravenously (closed circles) or subcutaneously (open circles) to eight and ten healthy male volunteers, respectively. MAP Mean arterial pressure.

Fig. 3 Mean (SD) adrenaline and noradrenaline concentrations in plasma after administration of 1 μg/kg of dexmedetomidine intravenously (closed circles) to eight or subcutaneously (open circles) to ten healthy male volunteers.

Fig. 4 Mean (SD) subjective assessment scores (vigilance and performance, visual analog scales, VAS) after administration of 1 μg/kg of dexmedetomidine intravenously (closed circles) to eight or subcutaneously (open circles) to ten healthy male volunteers.

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Table 1. Pharmacokinetic parameters after 1 µg/kg dose[1] of dexmedetomidine administered intravenously and subcutaneously in 10 healthy volunteers.

Parameter	Intravenous	Subcutaneous	P-value
C_{max} (ng/ml)	2.42 (0.36)	0.30 (0.1)	< 0.001
t_{max} (h)	0.17 (0.08-0.17)	0.25 (0.25-4)	0.013
AUC_{0-10} (ng·min/l)	117.3 (20.2)	74.4 (21.2)	< 0.001
$AUC_{0-\infty}$	120.5 (21.0)	108.5 (40.0)[2]	0.004
Cl/F (l/hr)	-	54.2	-
V_z/F (l)	-	92.8 (9.9)	-
Cl (l/hr)	40.6	-	-
Vss (l)	92.8 (9.9)	-	-
$t_{1/2}$ (min)	1.9 (0.25)	3.8 (0.89)	< 0.001
F (%)[3]	-	80.9 (48.6-96.6)	-

Data are given as mean and SD, except for t_{max} data, which are given as median and range.

C_{max}, peak plasma concentration; t_{max}, time to peak plasma concentration; AUC_{0-10}, area under dexmedetomidine plasma concentration–time curve 0 to 10 hours after dexmedetomidine dose; $AUC_{0-\infty}$, area under dexmedetomidine plasma concentration–time curve extrapolated to infinity; CL/F, Apparent oral clearance; V_z/F, apparent volume of distribution during elimination; CL, plasma clearance of midazolam; Vss, steady-state volume of distribution; F, oral bioavailability; $t_{½}$, elimination half-life.

[1]Dose was given as a 10 minutes long constant infusion

[2]In average, 28.6% (12.2) of $AUC_{0-\infty}$ was extrapolated

[3]Calculation of subcutaneous bioavailability was based on 8 subjects

Figure1

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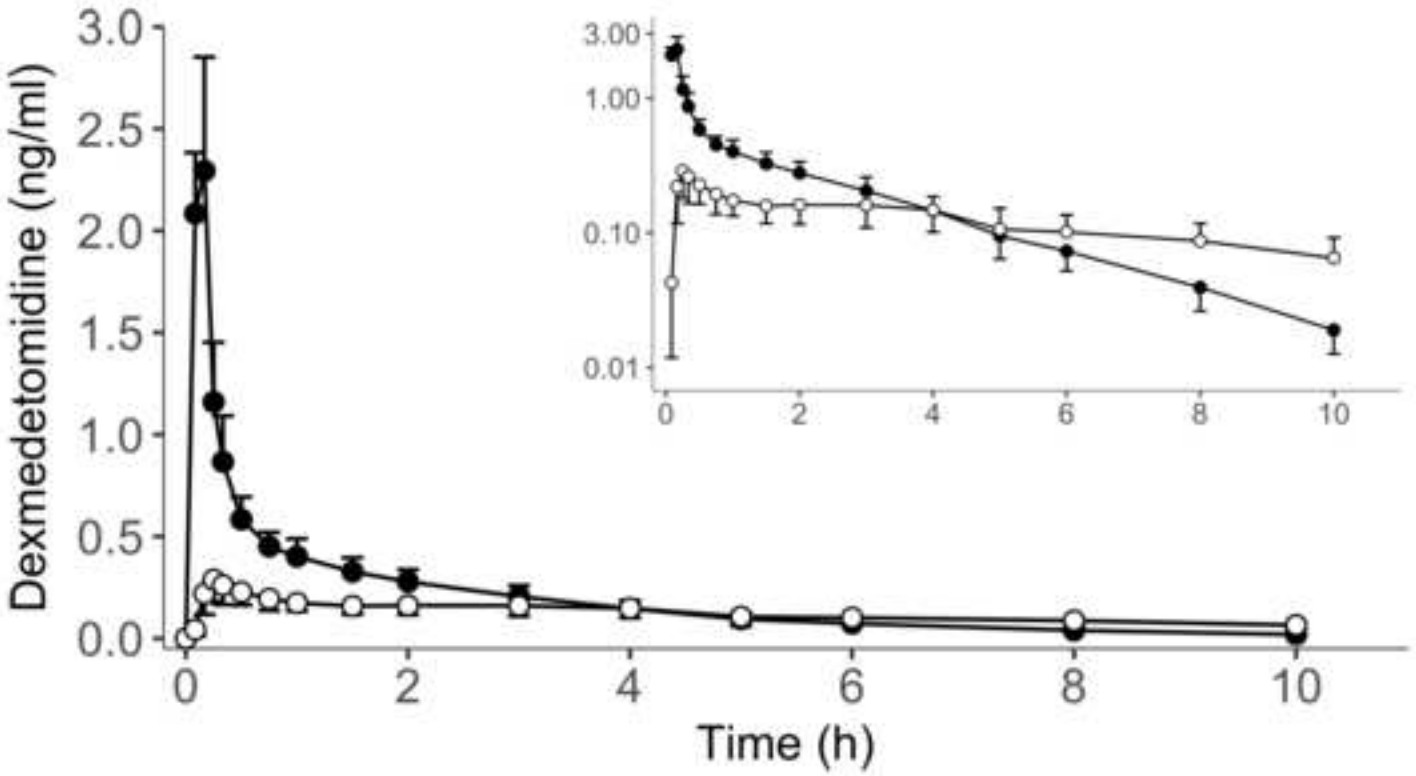

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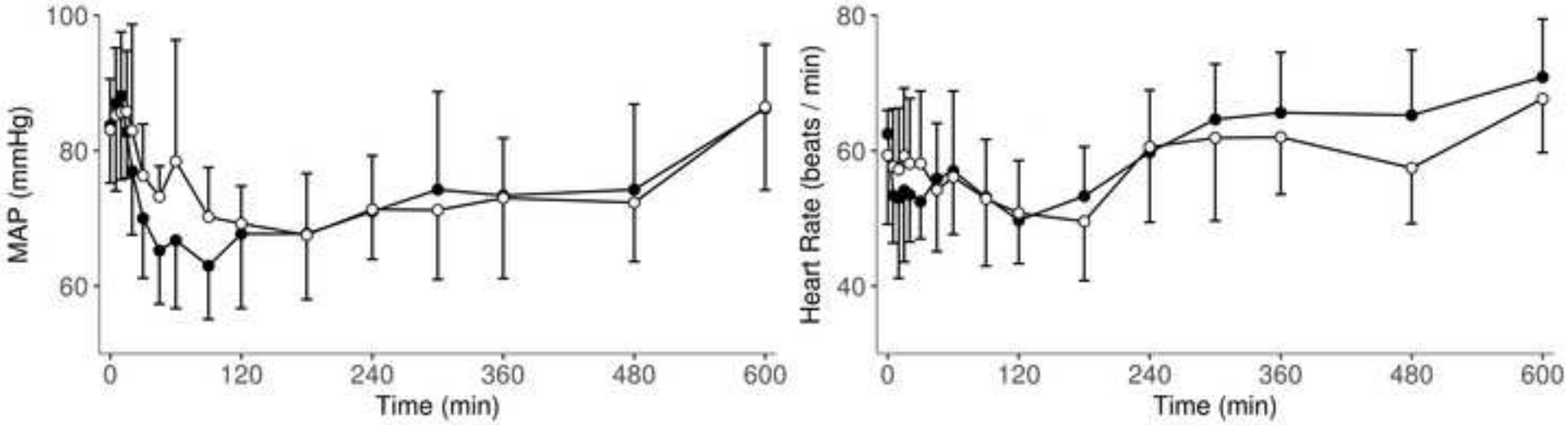

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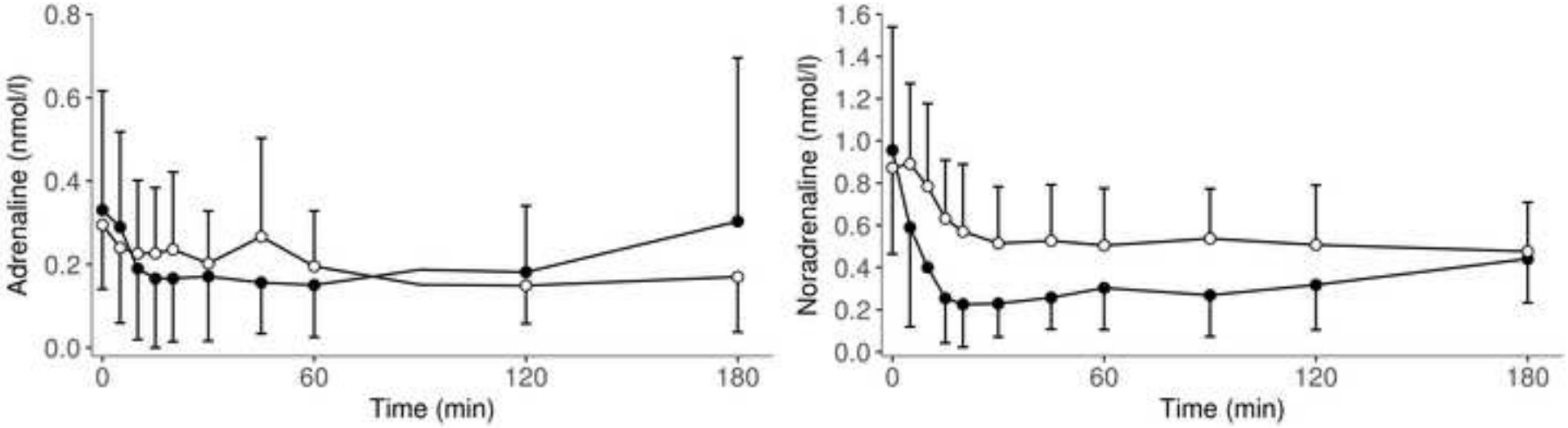

Figure4

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