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Repeated dexmedetomidine infusions, a postoperative living-donor liver transplantation patient

Katsuyuki Terajima[1], Shinhiro Takeda[1], Nobuhiko Taniai[2], Keiji Tanaka[3], Yutaka Oda[4], Akira Asada[4], and Atsuhiro Sakamoto[1]

[1] Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan
[2] First Department of Surgery, Nippon Medical School, Tokyo, Japan
[3] Critical Care Unit Division, Nippon Medical School, Tokyo, Japan
[4] Department of Anesthesiology and Intensive Care Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan

Abstract
Here we report on a postoperative living-donor liver transplantation (LDLT) patient who received nightly infusions of dexmedetomidine (DEX), a specific α2-adrenergic receptor agonist, to treat agitation and insomnia during an intensive care unit stay. The infusion rate was adjusted according to the Ramsay sedation score. The actual plasma concentrations were higher than the values predicted by RugLoop software package simulation 9 h after the DEX infusion. However, all of the measurements were within the therapeutic range for DEX. Thus, DEX infusion could be safely used in the postoperative LDLT patient by employing a simple consciousness scale.

Key words α2 Agonist · Agitation · Liver transplantation · Ramsay score · Sedation

Introduction

Dexmedetomidine (DEX) is a specific α2-adrenergic receptor agonist [1], which has sedative and analgesic effects [2]. DEX has fewer effects on respiration [3] and cognitive function than other agents used for postoperative sedation, and this facilitates communication and cooperation between patients and physicians [4]. This drug is therefore of particular use in patients undergoing weaning from a ventilator or after extubation in the intensive care unit (ICU).

The pharmacokinetics of DEX are largely influenced by liver rather than renal function [5]. Liver dysfunction may occur postoperatively in living-donor liver transplantation (LDLT) patients, as only 50% of the standard liver volume is usually transplanted to the recipient, and hypoperfusion and rejection of the graft or tissue can occur. Here we report the case of an LDLT patient who was treated with nightly infusions of DEX as a sedative during an ICU stay.

Address correspondence to: K. Terajima
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Case presentation

Written informed consent was obtained for the infusion of DEX for more than 24 h and for the reporting of this case. A 47-year-old female patient underwent LDLT involving a left-lobe graft in order to treat primary biliary cirrhosis. The grafted tissue weighed 495 g and corresponded to an estimated 46.1% of the patient's standard liver volume [6]. After the operation, the patient was transferred to the ICU and given ventilatory support.

Continuous infusions of fentanyl and midazolam were used for sedation and analgesia. On the second postoperative day (POD), continuous DEX infusion began while the midazolam infusion was discontinued. After extubation, the patient's blood gas values showed no deterioration. Propofol was given to treat emergent agitation, and following the DEX infusion to prevent agitation and sleeplessness during the night. The degree of sedation was measured hourly by a nurse, using the Ramsay sedation score, and the infusion rate was regulated at 0.1 to 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$, based on the Ramsay score [2 to 4]. On the following morning (the third POD) the patient remained calm even after the DEX infusion had ceased. The patient complained of sleeplessness and a desire to sleep the following night. Accordingly, DEX was infused during the night. Subsequently, DEX was only infused between 20.00 h and 05.00 h while the patient remained in the ICU. The infusion rates are shown in Table 1.

On the fifth to sixth POD, blood samples were drawn at the following time points: before the start of DEX infusion; 1, 2, 3, and 9 h after the DEX infusion began; and 1, 2, 3, and 8 h after the DEX infusion ceased. The plasma concentrations of DEX were measured using a

Table 1. Infusion rate of dexmedetomidine, and Ramsay scores and Child-Pugh scores

Postoperative day	1	2	3	4	5	6	7	8	9	10	11
Infusion rate of DEX ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	0	0–0.5	0.3	0.3–0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5
Ramsay score before infusion	4	1	1	2	1	2	2	2	2	2	2
Ramsay score during infusion		1–5	2–4	2–4	2–3	2–4	2–4	2–3	2–4	2–4	2–4
Ascites	2+	2+	2+	2+	2+	2+	2+	2+	2+	2+	2+
Bilirubin concentration ($mg \cdot dl^{-1}$)	6.6	6.6	6.7	8.4	7.4	6.1	5.2	4.7	4.4	3.9	4.1
Prothrombin time (%)	26	34	45	52	43	42	51	49	43	43	50
Hepatic encephalopathy	4	3	2	2	2	2	1	1	1	0	0
Albumin concentration ($g \cdot dl^{-1}$)	3.6	3.3	3.4	4.1	4.1	4.3	4.1	4.9	5.3	5.2	5.2
Child-Pugh score	13	14	12	11	11	11	11	11	11	10	10

Dexmedetomidine was infused only between 20.00 and 05.00 h while the patient remained in the intensive care unit
DEX, dexmedetomidine

previously reported method [7]. The lower limit of DEX quantitation was 50 $pmol \cdot ml^{-1}$, and the intraassay and interassay variations were less than 8% throughout the range (50–5000 $pmol \cdot ml^{-1}$). Values are means of duplicate measurements. The predictive plasma concentration of DEX was estimated using the RugLoop software package (version 3.28; University Hospital, Ghent, Belgium). The measured (and predictive) plasma concentrations of DEX (in $pmol \cdot ml^{-1}$) at 1, 2, 3, and 9 h after the DEX infusion began, and 1, 2, 3, and 8 h after the DEX infusion ceased were 0.22 (0.22), 0.23 (0.29), 0.34 (0.35), 1.14 (0.62), 0.59 (0.43), 0.46 (0.38), 0.38 (0.34), and 0.06 (0.19), respectively.

On the sixth POD, the cardiac index and indocyanine green elimination values were measured using the DDG-3300 system (Nihon Kohden, Tokyo, Japan). An indocyanine green elimination test showed an indocyanine green disappearance rate (K value) of 0.156 (normal range, 0.168 to 0.232) and 10.2% retention in 15 min. The heart rate was 99 bpm, and the cardiac index was 3.87 l/min per m^2.

After the DEX infusion, the patient remained calm and was able to cooperate in all examinations and treatments in the ICU.

Discussion

Repeated nightly infusions of DEX were safely administered to an LDLT patient in the ICU, using a simple sedation scale. Adverse effects based on repeated DEX infusion were not observed in our patient. The actual DEX plasma concentration was about two times greater than the predicted value at the end of the DEX infusions; however, the measured value was within the therapeutic range. The plasma concentration might be expected to rise above the simulated value during long-term DEX infusion. The pharmacokinetic parameters of DEX in postoperative patients in the ICU were previously reported to be similar to those in healthy volunteers [8]. Both liver function and the cardiac index [9] can affect the pharmacokinetics of DEX. Postoperative liver-transplantation patients generally have a fairly normal hemodynamic state. However, several days after transplantation (for example, during a stay in an ICU), these patients usually show hyperdynamic circulation, as a result of means used to prevent hepatic artery thrombosis, the maintaining of the graft circulation, and the clearance [10,11].

Recently, some clinical reports of prolonged DEX infusion in children [12], in the treatment of sedation-induced withdrawal [13], and in postoperative patients [14] have been published. No rebound sequelae occurred on the discontinuation of the DEX infusion. Adverse cardiovascular events were nearly all confined to the initial loading dose period of DEX.

The Ramsay score is somewhat limited in its evaluation of agitated behavior [15]; although it did not sufficiently express the level of agitation observed in our patient, it was useful for avoiding excess DEX levels in plasma.

In summary, repeated nightly infusions of DEX were useful for sedation in a postoperative LDLT patient. The use of a simple sedation score can avoid the problem of excess plasma DEX concentrations, even if the drug is repeatedly infused overnight.

References

1. Aantaa R, Kallio A, Virtanen R (1993) Dexmedetomidine, a novel alpha 2-adrenergic agonist. A review of its pharmacodynamic characteristics. Drugs Future 0:49–56
2. Angelini G, Ketzler JT, Coursin DB (2001) Use of propofol and other nonbenzodiazepine sedatives in the intensive care unit. Crit Care Clin 17:863–880
3. Venn RM, Hell J, Grounds RM (2000) Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit Care 4:302–308
4. Venn R, Bradshaw C, Spencer R, Brealey D, Caudwell E, Naughton C, Vedio A, Singer M, Feneck R, Treacher D, Willatts SM, Grounds RM (1999) Preliminary UK experience of

dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 54:1136–1142
5. De Wolf AM, Fragen RJ, Avram MJ, Fitzgerald PC, Rahimi-Danesh F (2001) The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg 93:1205–1209
6. Urata K, Kawasaki S, Matsunaami H, Hashikura Y, Ikegami T, Ishizone S, Momose Y, Komiyama A, Makuuchi M (1995) Calculation of child and adult standard liver volume for liver transplantation. Hepatology 21:1317–1321
7. Tanaka K, Oda Y, Funao T, Takahashi R, Hamaoka N, Asada A (2005) Dexmedetomidine decreases the convulsive potency of bupivacaine and levobupivacaine in rats: involvement of 2-adrenoceptor for controlling convulsions. Anesth Analg 100:687–696
8. Venn RM, Karol MD, Grounds RM (2002) Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. Br J Anaesthesia 88:669–675
9. Dutta S, Lal R, Karol MD, Cohen T, Ebert T (2000) Influence of cardiac output on dexmedetomidine pharmacokinetics. J Pharm Sci 89:519–527
10. Vaughan RB, Angus PW, Chin-Dusting JP (2003) Evidence for altered vascular responses to exogenous endothelin-1 in patients with advanced cirrhosis with restoration of the normal vasoconstrictor response following successful liver transplantation. Gut 52:1505–1510
11. Cao H, Wu Z, Zhang X, Chen Z, Kuang Y (2003) Changes in systemic splanchnic hemodynamics after orthotopic liver transplantation in cirrhotic rats. Chin Med J 113:1108–1111
12. Hammer GB, Philip BM, Schroeder AR, Rosen FS, Koltai PJ (2005) Prolonged infusion of dexmedetomidine for sedation following tracheal resection. Paediatr Anaesth 15:616–620
13. Multz AS (2003) Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. Anesth Analg 96:1054–1055
14. Venn M, Newman J, Grounds M (2003) A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. Intensive Care Med 9:201–207
15. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK (2002) The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 166:1338–1344