International Journal of Obstetric Anesthesia (2012) **21**, 339–347
0959-289X/$ - see front matter
http://dx.doi.org/10.1016/j.ijoa.2012.06.010

ORIGINAL ARTICLE

ELSEVIER
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Maternal and preterm fetal sheep responses to dexmedetomidine

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ABSTRACT

Background: The α_2 adrenergic receptor agonist dexmedetomidine has some unique pharmacologic properties that could benefit pregnant patients (and their fetuses) when they require sedation, analgesia, and/or anesthesia during pregnancy. The purpose of the present study was to delineate maternal and fetal responses to an intravenous infusion of dexmedetomidine.

Methods: This study was conducted on surgically-recovered preterm sheep instrumented for physiologic recording and blood sampling. Maternal and fetal cardiovascular and blood gas parameters and fetal cerebral oxygenation levels were recorded before, during, and after 3 h of dexmedetomidine infusion to the ewe at a rate of 1 μg/kg/h.

Results: Drug infusion produced overt sedation but no apparent respiratory depression as evidenced by stable maternal arterial blood gases; fetal blood gases were also stable. The one blood parameter to change was serum glucose, By the end of the 3-h infusion, glucose increased from 49 ± 10 to 104 ± 33 mg/dL in the ewe and from 22 ± 3 to 48 ± 16 mg/dL in the fetus; it declined post-drug exposure but remained elevated compared to the starting levels (maternal, 63 ± 12 mg/dL, $P = 0.0497$; and fetal, 24 ± 4 mg/dL, $P = 0.012$). With respect to cardiovascular status, dexmedetomidine produced a decrease in maternal blood pressure and heart rate with fluctuations in uterine blood flow but had no discernable effect on fetal heart rate or mean arterial pressure. Likewise, maternal drug infusion had no effect on fetal cerebral oxygenation, as measured by *in utero* near-infrared spectroscopy.

Conclusions: Using a clinically-relevant dosing regimen, intravenous infusion of dexmedetomidine produced significant maternal sedation without altering fetal physiologic status. Results from this initial acute assessment support the conduct of further studies to determine if dexmedetomidine has clinical utility for sedation and pain control during pregnancy.

Keywords: Dexmedetomidine; Fetus; Near-infrared spectroscopy; Obstetrical anesthesia; Pregnant sheep

Introduction

The need for non-obstetric related invasive therapeutic or diagnostic intervention can occur at any point during gestation.[1,2] For instance, women have a higher incidence of abdominal disorders than men and amongst females of child-bearing age the incidence of emergent corrective surgery, such as appendectomy is unaffected by pregnancy status.[3] Pregnancy may also necessitate the use of invasive diagnostic procedures because non-invasive alternatives are contraindicated to avoid fetal exposure to radiation.[4] As a result, almost 100 000 women per year in the USA receive agents for sedation, anesthesia and pain control at some point during their pregnancy for non-obstetric related care.[5] Interest remains high in identifying drug regimens that optimize maternal comfort with minimal fetal impact.[6]

The α_2 adrenergic receptor (α_2AR) agonist dexmedetomidine was approved in 1999 by the Food and Drug Administration for sedation and pain control of intensive care patients. Reports continue to indicate the drug is efficacious in this setting.[7,8] From this initial indication, dexmedetomidine has also been used to provide intraoperative sedation.[9] Some research groups have identified inappropriate applications[10] or questioned its analgesic potency,[11] while others have even utilized dexmedetomidine to provide surgical anesthesia to select patient populations.[12]

In addition to its sedative, anxiolytic, and analgesic actions, dexmedetomidine (similar to other α_2AR agonists) can reduce the need for other procedural medications through synergistic effects on opioid and

Accepted June 2012
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benzodiazepine-based agents.[13] These effects are all produced with minimal respiratory depression. Collectively, this profile of activity continues to prompt evaluation of additional clinical applications,[14,15] ranging from facilitation of awake intubation,[16] to supplementation of sedation and pain control during craniotomy,[17] and sedation of pediatric patients.[18] As of now, these investigations have not included significant cohorts of pregnant patients outside of women who were terminating their pregnancies[19] or single case reports[20–22] and pregnancy is an exclusion criteria for most currently active dexmedetomidine clinical trials (http://www.clinicaltrials.gov accessed 8th April 2012). Nonetheless, a number of dexmedetomidine's actions could be of potential benefit to fetuses of parturients requiring heavy sedation, anesthesia, and/or analgesia during pregnancy.[23]

One intriguing aspect is the potential for decreased dexmedetomidine-mediated cardiovascular depression in the mother and fetus because of the pregnancy-related decline in systemic maternal α_2AR sensitivity[24] even as the fetus has increasing numbers of α_2AR both systemically[25] and centrally.[26] Another intriguing aspect is the possibility that dexmedetomidine can protect the developing brain from excitotoxic injury.[27]

With this background, the goal of the present study was to delineate maternal and fetal physiologic responses to dexmedetomidine. The study was conducted on preterm pregnant ewes at gestational day 92, a time point approximately equivalent to the end of the second trimester in humans. The effects of dexmedetomidine on the preterm fetus are not known, yet this is a relevant developmental stage applicable to pregnant patients requiring sedation for non-obstetric related procedures. The ewes and fetuses were instrumented for recording cardiovascular activity and for monitoring arterial blood gas status. Because other α_2AR agonists have been reported to decrease uterine blood flow and fetal blood PO_2 levels,[28] and since the developing brain is arguably the most sensitive organ to a decline in oxygen availability, the fetuses were also instrumented with near-infrared spectroscopy (NIRS) probes to assess changes in fetal cerebral oxygenation during and after maternal drug administration.[29]

Methods

All aspects of the surgical and experimental protocols were approved by the Duke University Institutional Animal Care and Use Committee. Mix-breed time-dated Q-fever-negative preterm pregnant ewes were obtained from a commercial supplier. Upon arrival at Duke University, each ewe received an intramuscular injection of procaine penicillin G (1 200 000 IU). This penicillin regimen was repeated at 48 h intervals for the duration of the study. Ewes were housed individually and were allowed *ad libitum* access to food and water except for a 12–14 h fasting period before the surgical procedure; food was not withheld before dexmedetomidine exposure.

Instrumentation and catheterization of the ewe and fetus were performed at a mean gestational age of 90 ± 1 days. Surgery was conducted using a sterile technique and all components were cold-gas sterilized before installation. Following pre-sedation with subcutaneous midazolam 1 mg/kg, surgical anesthesia was induced with intravenous sodium thiopental 7 mg/kg and the trachea intubated. Surgical anesthesia was maintained with 1–2% isoflurane in oxygen delivered by a Narkomed 2B ventilation system (North American Dräger, Telford, PA, USA). To prevent aortocaval compression, ewes were placed (tilted) in the left lateral position.[30] Using standard surgical techniques, catheters were inserted into the left maternal femoral artery and left jugular vein and both the right and left fetal femoral arteries. An electronic flow probe (Transonic Systems Incorporated, Ithaca, NY, USA) was secured around the left uterine artery for recording uterine blood flow (UBF). The fetal head was then exteriorized and the skull was revealed following a midline scalp incision.

To install the NIRS fiberoptic bundle, a burr hole was drilled along the midline of the head, approximately 7.5 mm posterior to the coronal suture. The laser light source was gently inserted through this hole onto the dura and secured with the use of a custom-made 2 cm diameter metal plate and a series of small self-tapping screws. A second metal plate was used to secure the detector to the skull, 15 mm anterior to the light source. The fetus was then returned to the uterus. As the incisions were closed, a catheter was installed inside the amniotic cavity. The catheters, flow probe lead, and fiberoptic bundle were tunneled subcutaneously and then exteriorized through a small incision in the left flank of the ewe.

Upon completion of the surgery (3–4 h), bupivacaine 0.25% w/v was infused subcutaneously around the incision sites and the ewe returned to its pen. Nalbuphine hydrochloride, up to 1.0 mg/kg (or similar opioid) was administered intramuscularly to the ewe as needed to control postoperative pain. In addition to penicillin, prophylactic antibiotic therapy included two doses of gentamicin (ewe 80 mg intravenously, fetus 40 mg via the amniotic catheter) and daily maternal intravenous infusions of sulfamethoxazole 800 mg and trimethoprim 160 mg in 5% glucose. All ewes were allowed 48 h to recover from instrumentation before conducting the dexmedetomidine-exposure experiment.

On the day of experimentation, the ewe was placed in a support harness (Munks Livestock Sling Manufacturing Company, Anacortes, WA, USA) within a transportation cart. The arterial catheters were flushed with heparinized saline and then attached to force transducers (Transpac®; Abbott Laboratories, North Chicago,