

## Short communication

# Effects of propofol on gravid human uterine muscle

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Uterine contraction arrests bleeding from placental bed vessels, limiting peripartum bleeding. Drugs which interfere with this action need to be used with caution in obstetrics for fear of uterine atony. The depressant effect of inhalation anesthetics, especially halothane, on human uterine muscle activity has been well documented [1–6]. However, the effects of intravenous anesthetics on spontaneous uterine muscle activity have not been as well studied. Propofol (2,6-di-isopropylphenol) is used for balanced anesthesia, in outpatient surgery due to its convenience of fast recovery and earlier ambulation, and also in obstetric practice. It has so far been shown to have no adverse effects on maternal or fetal cardiovascular responses or acid-base status [7], and may be comparable to thiopental for the induction of general anesthesia for Caesarean section [8–9]. Since propofol is known to have a relaxant effect on vascular smooth muscle [10–11], and also on respiratory smooth muscle [12–13], we were interested in its effects on the myometrium. The effects of propofol on the spontaneous activity of human gravid uterine muscle *in vitro* are presented.

With institutional approval and informed consent, we took myometrial strips from the lower segment of uteri of 42 patients undergoing elective lower-segment Caesarian section (LSCS) under general endotracheal anesthesia (sodium thiopental, succinylcholine, atracurium, fentanyl/morphine analgesia, and 0.5% isoflurane). Myometrial strips (approximately 10 × 2 × 2 mm) were prepared and mounted in an organ bath

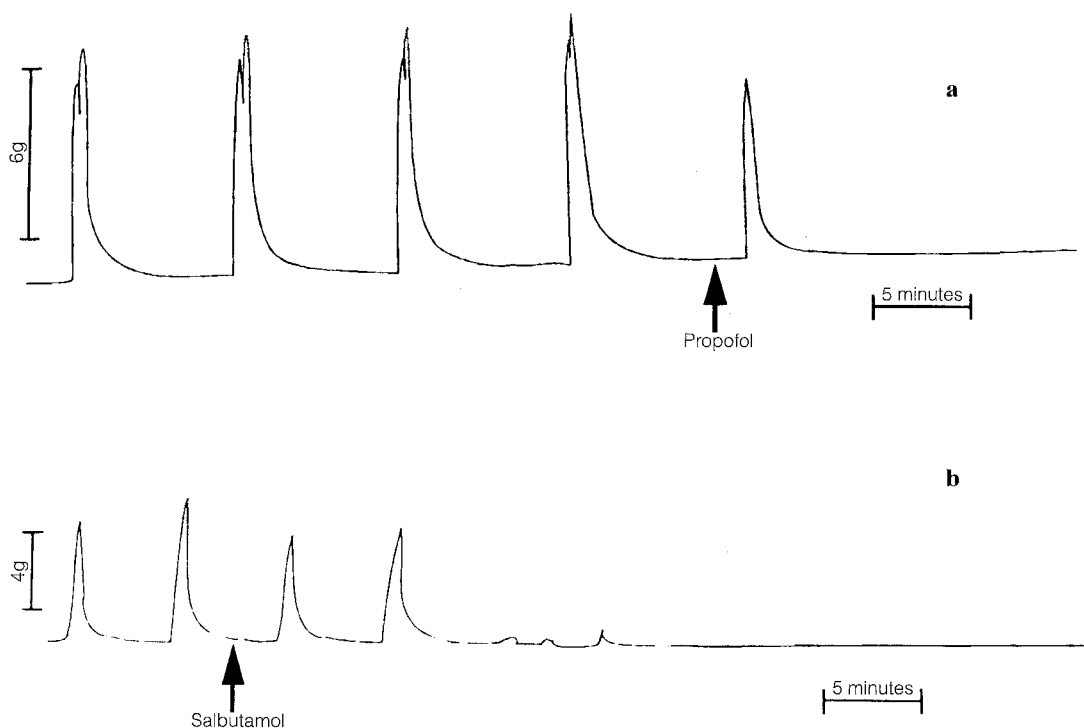
containing Krebs-Henseleit (KH) solution (composition in mM: NaCl 118, KCl 4.7, CaCl<sub>2</sub> 2.5, KH<sub>2</sub>PO<sub>4</sub> 1.1, MgSO<sub>4</sub> 1.2, glucose 4.5, NaHCO<sub>3</sub> 2.5; and pH 7.4), kept at 37°C and aerated by a mixture of 95% O<sub>2</sub> and 5% CO<sub>2</sub>. Each muscle strip was attached to an isometric force transducer and allowed to equilibrate until it contracted spontaneously (usually 1–1.5 h) under a resting tension of 1.5 g before the drugs were added. The responses were monitored by a Hewlett-Packard recorder (7702B, Hewlett-Packard, Andover, MA, USA). Propofol (Diprivan; ICI, Macclesfield, Cheshire, UK), 10% intralipid (vehicle for propofol), and salbutamol (Ventolin, Glaxo, Greenford, England) were studied independently and compared to control myometrial strips run in parallel without the drug.

Propofol was used at a final concentration of 3.4 × 10<sup>-4</sup> M in the organ bath, based on preliminary studies which showed less consistent responses at lower concentrations, while salbutamol organ bath concentrations were 2.1 × 10<sup>-5</sup> or 4.2 × 10<sup>-5</sup> M. Propranolol, prazosin, and yohimbine (Sigma, St. Louis, MO, USA) were used to define the possible mechanism of action of propofol. Patients who had received sympathomimetic/sympatholytic drugs preoperatively were excluded from the study. The interaction between oxytocin and propofol, and between oxytocin and salbutamol were studied by adding oxytocin (10 mU or 20 mU) into the organ bath 20 min after propofol or salbutamol. In another set of experiments, propofol or salbutamol was introduced after the myometrial strips had been artificially stimulated with oxytocin (10 mU). For a few strips (*n* = 6), washout of the drugs was achieved through constant replacement of the bath fluid at a rate of 1 ml·min<sup>-1</sup> to limit sudden weight changes, to determine, the reversibility of the effects of propofol.

Propofol 3.4 × 10<sup>-4</sup> M consistently depressed spontaneous uterine muscle activity (Fig. 1a). Salbutamol showed dose-dependent effects: at 2.1 × 10<sup>-5</sup> M, spontaneous activity was abolished in only 70% of the

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**Fig. 1.** **a** Effects of propofol on myometrial contraction. A representative tracing showing how propofol ( $3.4 \times 10^{-4}$ M) abolished spontaneous myometrial contractions in all cases. **b** Representative tracing showing the effects of salbutamol on spontaneously contracting myometrial strips. Salbutamol ( $4.2 \times 10^{-5}$ M) abolished myometrial contractions in all cases

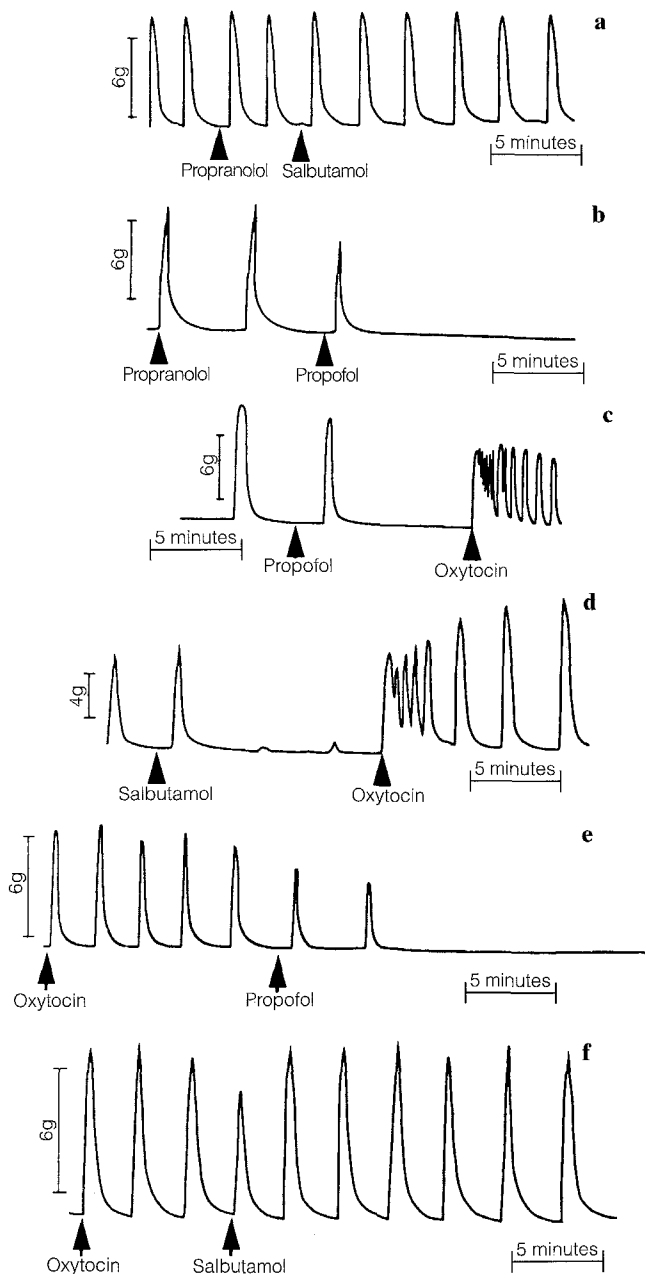
myometrial strips, while at a higher dose ( $4.2 \times 10^{-5}$ M) all responses were abolished; a typical tracing is shown only for the higher dose (Fig. 1b). Intralipid (10%) had no effect on uterine smooth muscle contraction when administered at a volume of 0.075 ml, the same volume as for propofol. The myometrial strips recovered spontaneously after 2–3 h washout of propofol.

Propranolol ( $7.7 \times 10^{-5}$ M) on its own had no effect on uterine muscle contraction but inhibited salbutamol-induced uterine muscle relaxation (Fig. 2a). Propranolol, however, had no effect on propofol-induced uterine muscle relaxation (Fig. 2b). The effect of propofol was similarly not affected by pretreatment of tissues with prazosin or yohimbine. Oxytocin stimulated uterine muscle contraction in the presence of propofol (Fig. 2c) or salbutamol (Fig. 2d). In myometrial strips pretreated with oxytocin, propofol inhibited, while salbutamol had no effect on, oxytocin-stimulated contraction (Fig. 2e and f, respectively).

Many inhalation anesthetics have been shown to have a direct depressant effect on uterine activity [1–3]. This report suggests that propofol shares this action in common with the inhalational agents. Propofol reduces arterial blood pressure partly as a result of a direct, negative inotropic action [14], and has a direct relaxant effect on vascular smooth muscle [11] and on airway smooth muscle [12–13]. In an attempt to establish the mechanism through which propofol abolishes

myometrial contractility, we used drugs with effects on adrenergic mechanisms, because of the well known involvement of both  $\beta$ - and  $\alpha$ -adrenergic systems in myometrial contractility [15–19], but none of them appeared to modify the effects of propofol. The interactions between propofol and oxytocin are noteworthy because pretreatment with propofol has no effect on subsequently administered oxytocin (Fig. 2c) while propofol suppresses oxytocin-induced contractions when administered afterwards (Fig. 2e). Clearly, the effects of propofol are different from those of salbutamol pre and post treatment which are reversed by oxytocin (Fig. 2d,f). The depressant effects of propofol on myometrial contraction may be part of a general, nonspecific relaxant/depressant effect.

Our results need not be seen as contradictory to the clinical reports that have suggested propofol as an acceptable alternative to thiopental for the induction of general anesthesia in obstetrics, without effect on uterine contractility or maternal blood loss [8–9]. The propofol concentration used was in the upper range of those achieved in clinical practice [20–21]. Propofol is rapidly eliminated from the body, and its effects are short-lived, whereas *in vitro* it was in contact with the tissue for a relatively longer time; but even with the high concentration and long exposure in the organ bath, the strips spontaneously recovered after propofol washout. This suggests that, were propofol to produce similar



**Fig. 2.** **a** Effects of propranolol on myometrial contraction and on the effects of salbutamol. Propranolol had no effect on myometrial activity, but it abolished the relaxant effects of subsequently administered salbutamol. **b** Typical tracing showing the effects of propranolol on the relaxant effects of propofol. Propranolol had no apparent effect on the relaxant effects of propofol on spontaneously contracting myometrial strips. **c** Effects of oxytocin on the relaxant effects of propofol. Oxytocin (10 or 20 mU·ml<sup>-1</sup>) reversed the relaxant effects of propofol; the tracing shown is for oxytocin 10 mU·ml<sup>-1</sup>. **d** Effects of oxytocin on the relaxant effects of salbutamol. As for propofol, oxytocin (10 or 20 mU·ml<sup>-1</sup>) reversed the relaxant effects of salbutamol. **e** A typical tracing for the effects of propofol on oxytocin-augmented myometrial contractions. Propofol abolished myometrial contractions in the presence of oxytocin. **f** Typical tracing showing the lack of effect by salbutamol on oxytocin-augmented myometrial contractions

results in vivo, they would be short-lived and the myometrium would recover thereafter with no attendant increase in blood loss. That oxytocin abolished the relaxant effects of propofol suggests that even when the action of propofol is established, administration of oxytocin would reverse its tocolytic effects. Thus, propofol could be used for induction of anesthesia for Caesarian section without fear of profound, long-lasting atony.

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