The effect of levcromakalim (BRL 38227) on bladder function in patients with high spinal cord lesions

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The effects of the potassium channel opener levcromakalim (BRL 38227) $7.5 \mu\text{g kg}^{-1}$ were examined on urodynamic variables and blood pressure during inflow and voiding cystometry in six high spinal cord lesion patients. Levcromakalim administration significantly increased the duration of bladder contraction (197 ± 128 s to 267 ± 167 s, $P < 0.05$) and also reduced blood pressure ($126 \pm 13/67 \pm 9$ mm Hg to $104 \pm 25/52 \pm 12$ mm Hg) but was without effect on other urodynamic parameters. Because of concerns about hypotensive responses, further studies involving higher doses of levcromakalim should be considered only if the drug was administered intravesically.

Keywords levcromakalim detrusor hyperreflexia inflow and voiding cystometry spinal cord lesion patients

Introduction

Detrusor hyperreflexia is a particular form of bladder instability frequently found in patients with high spinal cord lesions and characterised by an impairment of voluntary command of micturition, impairment or loss of bladder sensations, detrusor contraction on external mechanical stimulation and sometimes unco-ordinated micturition due to detrusor-sphincter dyssynergia [1]. Current treatment methods for detrusor hyperreflexia include bladder training, intermittent catheterisation, augmentation cystoplasty and the use of anticholinergic drugs. However, none of these treatments is completely successful and in many cases have unwanted side effects [2].

Cromakalim acts as a potassium channel opener in smooth muscle mediating relaxation in a number of smooth muscles including vascular smooth muscle [3] and the detrusor muscle of the bladder [4–7]. Cromakalim abolishes spontaneous bladder contractions in pigs [5], rats [8] and rabbits [9] with bladder instability, with little change in other urodynamic variables. Cromakalim also lowers blood pressure in pigs when administered in doses that suppress the unstable contractions [5].

Levcromakalim (BRL 38227) is the pharmacologically active 3S,4R enantiomer of cromakalim [10]. In this open pilot study the effect of levcromakalim $7.5 \mu\text{g kg}^{-1}$ intravenously was determined on urodynamic variables and blood pressure measured during inflow and voiding cystometry in high spinal cord lesion patients with detrusor hyperreflexia.

Methods

Six males aged 24–41 years (71 ± 7 kg) with high spinal cord injury at or above T10 and with established reflex micturition entered this study. All the patients had normal biochemistry, haematology, blood pressure, ECG and urinalysis results and were normal on physical examination except for symptoms resulting from the spinal lesion. The purpose of the study was explained to all patients and written informed consent was obtained. The protocol was approved by the Austin Hospital Ethics Committee.

The urodynamic procedure has been described previously [11] and involved bladder filling at a rate of

20 ml min⁻¹ with simultaneous recording of bladder pressure, rectal pressure and urine flow rate on a LifeTech transducer tracing recorder (LifeTech, USA) and Lab Mac Superscope 1.6 System. Infused and voided volumes were also recorded and the interval between detrusor contractions, between voids and between contraction and voiding were derived from the pressure traces. At least three cycles of bladder contractions were carried out before the drug infusion and were then repeated after levromakalim 7.5 µg kg⁻¹ infused over 10 min via a Venflon cannula inserted into an antecubital vein. Blood pressure, heart rate and ECG were recorded continuously using a Finapres BP Monitor (Ohmeda, USA) and Hewlett Packard 78351A (for ECG). The average blood pressure was determined over three intervals: a 10 min period prior to drug infusion, the final 5 min of the infusion and a 10 min period after drug infusion. The blood pressure changes accompanying bladder contractions were not included. All patients except for one were hospitalised overnight for observation.

Results

The levromakalim infusion did not alter the infused volume which precipitated detrusor contraction, the interval between contractions or voidings nor did it significantly alter the volume voided, or the resting and maximal bladder pressure (Table 1). There was, however, an increase in the duration of contraction by 36% following levromakalim infusion (Table 1).

Levromakalim produced a rapid fall in supine blood pressure from a pre-infusion level of 126 ± 13/67 ± 9 mm Hg to 104 ± 25/52 ± 12 mm Hg ($P < 0.05$ systolic, $P < 0.001$ diastolic) during the second half of the infusion. In the period immediately after the infusion blood pressure returned to 118 ± 24/63 ± 11 mm Hg. Heart rate increased from 59 ± 15 beats min⁻¹ to 76 ± 17 bpm ($P < 0.05$) during infusion and remained above baseline after infusion (68 ± 16, $P < 0.05$).

In all patients the start of each bladder contraction was usually accompanied by a few seconds of hyperreflexia indicated by an increase in blood pressure. In five patients this was asymptomatic but one patient experienced flushing associated with the hyperreflexia. In one patient the fall in blood pressure was dramatic (from baseline 112/55 to 72/40 mm Hg). This fall persisted after the end of the study but recovered to baseline in the next 5 h. No other adverse events were observed either during the study or during the following 24 h.

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Table 1 Summary of urodynamic parameters (mean ± s.d.) pre and post levromakalim 7.5 µg kg⁻¹

	Pre	Post
Infused volume (ml min ⁻¹)	162 ± 83	147 ± 74
Voided volume (ml)	143 ± 62	135 ± 62
Pressures (cm H ₂ O)		
Resting	1 ± 13	1.5 ± 15
Maximum	70 ± 32	63 ± 32
Intervals (s)		
E-S	485 ± 248	441 ± 223
C-C	572 ± 328	565 ± 262
Duration of contractions (s)	197 ± 128	267 ± 167*

* $P < 0.05$ (ANOVA).

Intervals: E-S Interval between end of previous and start of next voiding.

C-C Interval between contractions.

Infused volume: Volume of normal saline infused in urinary bladder during E-S interval at rate 20 ml min⁻¹.

Voided volume: Volume of urine voided during 1 contraction.

Pressures: Resting – pressure in bladder before contraction.

Maximum – subtraction of peak and resting pressures.

Data analysed by ANOVA with one within subject variable.

Discussion

In *in vitro* studies cromakalim has been shown to inhibit spontaneous and exogenously induced contractile activity of hyperreflexic human detrusor muscle [5, 7]. Nurse *et al.* [7] have further referred to an unpublished study that reported a clinical benefit of an unknown dose of levromakalim in some patients with detrusor instability or hyperreflexia. In our study, levromakalim 7.5 µg kg⁻¹ i.v. failed to alter urodynamic parameters associated with the hyperreflexic response in any clinically meaningful way. Higher doses may be more effective but are likely to be accompanied by falls in blood pressure.

Intravesical instillation of oxybutynin chloride is an effective treatment of detrusor hyperreflexia that minimises systemic side effects [12, 13]. As intravesically administered cromakalim inhibited spontaneous activity in the rabbit urinary bladder in a rabbit hyperreflexic model without any change in blood pressure [9], studies with intravesical administration of levromakalim in man may demonstrate a clinical benefit without adverse side effects.

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