89-53
PA-PBG-083

Br. J. clin. Pharmac. (1989), **28**, 715–717

Lithium inhibits human sperm motility *in vitro*

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Lithium is a widely prescribed drug used for the treatment of bipolar affective illness. Previous reports on its effects on sperm motility and male fertility are conflicting. The effect of lithium on human sperm motility was examined *in vitro* using the modified trans-membrane migration method. This technique takes account of the dilution of lithium that occurs during the incubation. Lithium inhibits human sperm motility *in vitro* in concentrations comparable with those reported to be achieved in semen after oral administration.

Keywords lithium sperm motility

Introduction

Sperm motility is one of the important parameters of sperm function. Immotile sperm, whether living or dead, cannot penetrate the cervical mucus (Tampion & Gibbons, 1963) or fertilize the ovum (Blandau & Rumery, 1964). However sperm motility is not the only determining factor of successful fertilization (Amelar *et al.*, 1980).

Reports on the effect of lithium on sperm motility and male fertility are few and conflicting. Macleod *et al.* (1949) found that lithium, in relatively small concentrations, inhibits the metabolism and motility of human spermatozoa. Both aerobic and anaerobic pathways of glycolysis were affected. There was a concentration-dependent inhibition of sperm motility with almost complete immobilisation of motility at a concentration of 25 mmol l^{-1}. However, more recent *in vitro* studies, using the turbidimetric method, could demonstrate no significant effect of lithium on sperm motility (Levin *et al.*, 1981a,b). Reports of the *in vivo* effect of lithium on sperm motility and male fertility in patients were equally conflicting (Kolomaznick *et al.*, 1981; Raboch *et al.*, 1981).

Studies on sea urchin spermatozoa showed an inhibitory effect of lithium on sperm motility (Gibbons & Gibbons, 1984). A concentration of 6 mmol of lithium was sufficient to inhibit the microtubule-based movement of reactivated, demembranated sea urchin spermatozoa (Gibbons & Gibbons, 1984). This inhibition was completely reversible by 100-fold dilution with fresh reactivating solution containing no lithium. The trans-membrane migration ratio (TMMR) method (Hong *et al.*, 1981) has been found to relate closely to visual methods for assessing sperm motility (Lee *et al.*, 1989). Using the original method it was found that lithium inhibited sperm motility, the concentration inhibiting sperm motility by 50% (EC_{50}) being 63 mmol l^{-1}) (Grech *et al.*, 1983). However, this method did not take into consideration the dilution of lithium by buffer that occurred in the lower chamber during the incubation period. A modified TMMR technique (Raoof *et al.*, 1987) provides exposure of the semen to a constant concentration of lithium throughout the 2 h incubation time. This is achieved by placing in the lower chamber a buffer containing the same concentration of the drug as in the upper chamber. This technique was used in the study reported here to examine the effect of lithium on human sperm motility *in vitro*.

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Methods

Semen samples were obtained from seven healthy volunteers by masturbation. All samples had sperm concentrations higher than 15×10^6 ml^{-1} and more than 20% of progressive forward motility, these values being essential in order to obtain consistent results (Hong, 1982). They were left to liquify at room temperature (21° C) for 30 min before examination. All samples were produced in the laboratory and examined within 1 h.

A 1 M stock solution of lithium chloride was prepared by dissolving 4.24 g of lithium chloride (molecular weight 42.4) in 100 ml phosphate buffer saline (PBS). The pH was adjusted to 7.4. Further dilution with PBS of this solution was made to prepare two sets of solutions. One set (1.5, 3.0, 7.5, 15.0, 30.0, 75.0, 150.0, and 300.0 mmol l^{-1}) to be added to semen aliquots, and another set (0.5, 1.0, 2.5, 5.0, 10.0, 25.0, 50.0, and 100.0 mmol l^{-1}) to be placed in lower chambers.

To examine the effect of lithium on sperm motility, the modified trans-membrane migration ratio (TMMR) method (Raoof *et al.*, 1987) was used. In this modification of the technique, lithium in buffer was put in both the upper and the lower chambers. To 100 µl of semen, 50 µl of the lithium buffer solution was added (thus the drug was diluted by a factor of 1 : 3). A 100 µl aliquot of this mixture was put in the upper chamber. In the lower chamber 2 ml of buffer containing the same final concentrations of lithium as in the upper chamber were introduced. The tubes were incubated for 2 h and then the sperm motility was expressed as a percentage of a control which was included in the experiment by incubating the sperm with PBS only.

Results

The results show clear inhibition of sperm motility by lithium. Figure 1 is a semilogarithmic plot of lithium concentration (mmol l^{-1}) *vs* TMMR expressed as a percentage of the control. The EC_{50} for the inhibitory effect of lithium, calculated from the semilogarithmic plot, was 6.4 mmol l^{-1}.

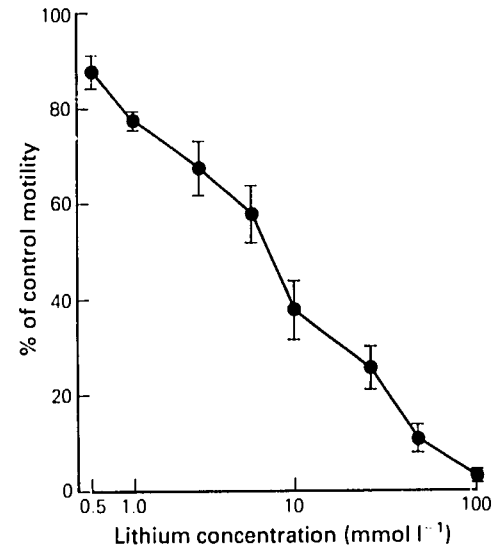

Figure 1 A semilogarithmic plot of the effect of lithium on sperm motility using the modified trans-membrane migration ratio (TMMR) method. The points represent the mean ± s.e. mean (n = 7).

Discussion

The results of this experiment show a concentration-dependent inhibition by lithium on sperm motility. Gibbons & Gibbons (1984) found that 6–8 mmol l^{-1} lithium was sufficient to cause complete cessation of flagellar movement. This concentration is comparable with the concentration causing 50% inhibition of sperm motility in the above study. Reasons for this discrepancy may be due to species differences and to the use by Gibbons & Gibbons (1984) of demembranated, reactivated spermatozoa which were more sensitive to the effect of drugs. This immobilizing effect of lithium was completely reversible by 100-fold dilution of the immobilized sperm with fresh (reactivating) solution containing no lithium. This reversibility might also be the cause of the wide difference between the results obtained in our study (EC_{50} of 6.4 mmol l^{-1}) and the results obtained by using the original TMMR technique (63 mmol l^{-1}) (Grech *et al.*, 1983).

Lithium is widely distributed throughout body tissues when given orally. Its concentrations in semen after oral administration are about double those in blood. Values for lithium concentrations as high as 3.2 mmol l^{-1} have been observed in semen of some individual healthy volunteers treated with therapeutic doses of lithium (Raoof, 1988). This value would correspond to a reduction of about 25% in sperm motility. From these present results, it is possible to speculate that lithium may affect sperm motility in some patients on chronic lithium therapy. Other *in vivo* studies about the effect of lithium on sperm motility and male fertility are conflicting.

Raboch *et al.* (1981) found no abnormality in sperm count, motility and morphology of semen samples obtained from 10 patients on lithium therapy. However, Kolomaznick *et al.* (1981) reported significantly worse spermatogram findings in terms of sperm count and motility of samples obtained from nine patients on lithium and neuroleptics drugs. There is some evidence that various parameters of motility of spermatozoa relate to the ability to fertilize the ovum (Amelar *et al.*, 1980). The present findings suggest that further studies on patients receiving lithium therapy are needed, using objective measurements of sperm motility in which semen quality in terms of sperm count, motility and morphology should be studied before and after starting lithium treatment.

We gratefully acknowledge the support of the Arabian Gulf University (Bahrain), Family Health International, the Peel Medical Research Trust and the Lawson Tait Medical and Scientific Research Trust.

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(*Received 7 February 1989, accepted 23 August 1989*)

Br. J. clin. Pharmac. (1989), **28**, 718–721

The pharmacokinetics of xamoterol in liver disease

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The pharmacokinetics of xamoterol, a β_1-adrenoceptor partial agonist, have been studied in patients with liver disease and a group of age- and sex-matched normal controls. No significant differences were observed after the oral administration of xamoterol 200 mg. The low bioavailability of xamoterol was confirmed (6.1% in patients, 6.9% in controls). After i.v. xamoterol 0.2 mg kg^{-1}, no significant differences between the groups were observed. A small increase in the terminal plasma elimination half-life ($t_{1/2}$) was observed in patients when compared with controls (15.3 ± 6.4 *vs* 8.4 ± 2.8 h, mean ± s.d., $P = 0.08$). Renal clearance accounted for about 50% of total clearance in patients and about 30% in controls. It is suggested that in patients with heart failure, hepatic dysfunction would probably not influence xamoterol disposition.

Keywords xamoterol pharmacokinetics liver disease

Introduction

Xamoterol ((±)-1-(4-hydroxyphenoxy)-3-(2-(4-morpholine carbonamido) ethylamino)-propan-2-ol, hemifumarate); ICI 118, 587; Corwin, ICI Pharmaceuticals) is a β_1-adrenoceptor partial agonist (Nuttall & Snow, 1982). In normal man, resting heart rate is increased (Hashimoto *et al.*, 1986) but heart rate at high levels of exercise is reduced (Harry *et al.*, 1981), indicating β-adrenoceptor agonist activity when levels of sympathetic tone are low, and β-adrenoceptor antagonist activity when levels are high (Detry *et al.*, 1983; Sato *et al.*, 1987). Systolic time intervals are reduced, indicating positive inotropic activity (Marlow *et al.*, 1982; Hashimoto *et al.*, 1986). This profile of action is potentially beneficial in the treatment of patients with heart failure (Rousseau *et al.*, 1983), and recent clinical trials have confirmed the efficacy of xamoterol in this condition (German and Austrian Xamoterol Study Group, 1988). As patients with congestive cardiac failure frequently have hepatic dysfunction, and as xamoterol has been reported to have a low bioavailability after oral administration, we have compared the kinetics of xamoterol after oral and i.v. administration in patients with liver disease and in normal volunteers.

Methods

Subjects

Observations were made on six patients with liver disease and six control subjects. The patients all had clinical and biochemical evidence of liver disease (see Table 1). The mean age of the group was 56.5 years (range 29–69) and the mean body weight was 68.5 kg (range 54–90.5). After each patient had been studied, an age- and sex-matched volunteer was recruited. The mean age of the volunteers was 56 years (range 34–68) and the mean body weight was 72.6 kg (range 58–82.3). No volunteer had any clinical or biochemical evidence of liver disease, and none gave any history of alcohol abuse. Patients were excluded from the study on the following grounds: severe

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