

SKY0402 (bupivacaine) does not prolong QTc interval in a thorough QT/QTc study in healthy volunteers

3P-64

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Introduction

Bupivacaine has been marketed since 1987 but no conclusive data on cardiac safety of its use as a local anaesthetic is available. Only two studies have reported a slight prolongation of QTc after doses of 48 mg (27 msec) and 75 mg (24 msec), respectively [1,2].

The duration of analgesic action of local anaesthetics is typically less than 12 hours [3]. A new formulation of slow release bupivacaine, SKY0402, given as a single local injection after surgery could provide adequate, continuous, and extended pain relief. SKY0402 consists of microscopic, spherical, lipid based particles (the DepoFoam® drug delivery system) which release drug over an extended period of time.

Aims

The purpose of this TQT study was to characterise the effect on QTc of single doses of SKY0402 300 mg, 450 mg, 600 mg and 750 mg compared to placebo on the largest time-matched mean QTc variation using a 400 mg dose of moxifloxacin as a positive control to confirm assay sensitivity.

Methods

Study Design

This study was performed in two parts in the same subjects.

Part 1 - single centre, randomised, double blind, placebo- and positive-controlled, double dummy (placebo and moxifloxacin randomised), five-way, cross-over study (300 mg & 450 mg). SKY0402 was administered in an ascending manner for safety reasons. The maximum dose of SKY0402 was chosen based on literature and the summary of product characteristics (SPC).

Part 2 - single centre, sequential dose, open-label study (600 mg & 750 mg). Higher doses were used as plasma concentrations from 300 mg and 450 mg were lower than expected.

SKY0402 or placebo was administered subcutaneously into the subcutaneous layer of the abdominal wall and Moxifloxacin or placebo were administered orally. ECG profiling was performed over a 24 hour period after each dose of study medication using 10 second 12-lead triplicate recording with further ECG recordings over a 96 hour period to accommodate the extended plasma half life of SKY0402. Adverse events were recorded from the first dose of study medication until follow-up.

Data Analysis and Statistical Methods

Measurement of the QT interval was performed automatically with subsequent manual on-screen over-reading using electronic callipers (MUSE CV® Interval Editor; GE Healthcare). The effect on the QT/QTc interval was analysed using the largest time-matched mean difference between moxifloxacin/SKY0402 and placebo. All on treatment values were corrected using time matched baseline values. Under blinded conditions QTcI was determined to be the best correction formula.

Subject Disposition

49 subjects in total were randomised in Part 1. Three subjects did not complete the study and one of these subjects withdrew consent and was replaced.

Of all subjects (48) included 47 were Caucasian and one subject was Hispanic; their mean age was 26±5 years. 34 subjects were male and 15 subjects were female, the mean BMI ranged from 19.1 and 29.0 kg/m².

Of the 46 subjects completing Part 1 of the study 16 were available for inclusion in Part 2 (mean age 27 ± 6 years; 10 subjects were male and 6 subjects were female; the mean BMI ranged from 20.3 to 27.1 kg/m²).

QTc Results

QTcI (Statistical analysis of change)

	Estimate (1)	95% CI (2)
Part 1		
Moxifloxacin 400 mg (N=48)	11.91 (1.21)	[9.87 ; 13.96]
SKY0402 300 mg (N=46)	-2.24 (1.00)	[-3.91 ; -0.56]
SKY0402 450 mg (N=47)	-2.45 (0.88)	[-3.92 ; -0.97]
Part 2		
SKY0402 600 mg (N=16)	-3.60 (2.16)	[-7.27 ; 0.07]
SKY0402 750 mg (N=16)	-7.67 (2.47)	[-11.9 ; -3.46]

(1): Estimate (standard error) of the adjusted changes differences;
(2): 95% CI of the adjusted changes differences

Table 1 QTcI (msec) change from P-baseline to P-postbaseline for moxifloxacin 400 mg, SKY0402 300 mg, SKY0402 450 mg, SKY0402 600 mg, SKY0402 750 mg and placebo

Effect of Moxifloxacin 400 mg on QTc

Mean QTcI was prolonged in subjects receiving moxifloxacin 400 mg compared with placebo (Table 1). This observation is consistent with previous findings at the study site [4,5] using the same clinical and ECG core laboratory infrastructure.

Effect of SKY0402 300 mg and 450 mg on QTc

No prolongation of mean QTcI was observed in subjects receiving either SKY0402 300 mg or 450 mg compared with placebo (Table 1).

Effect of SKY0402 600 mg and 750 mg on QTc

No prolongation of mean QTcI was observed in subjects receiving either SKY0402 600 mg or 750 mg compared with placebo (Table 1).

When heart rate was corrected using QTcF, a similar pattern of results was seen. The largest time-matched difference in QTcF was found to be 11.27 msec (moxifloxacin 400 mg), -1.77 msec (300 mg), -2.60 msec (450 mg), -2.85 msec (600 mg) and -6.24 msec (750 mg), respectively.

Safety Results

Safety and Tolerability

Moxifloxacin and SKY0402 were well tolerated by healthy subjects in both parts of the study. The majority of subjects reported AEs which were considered to be mild.

One serious adverse event (SAE) occurred during Part 1 which was not considered drug related: one subject was diagnosed with acute hepatitis A seven days after the administration of SKY0402 450 mg.

QTc vs PK Analysis

The relationship between QTcI and moxifloxacin plasma concentration (Figure 1) and the relationship between QTcI and SKY0402 plasma concentration (Figure 2) was analysed.

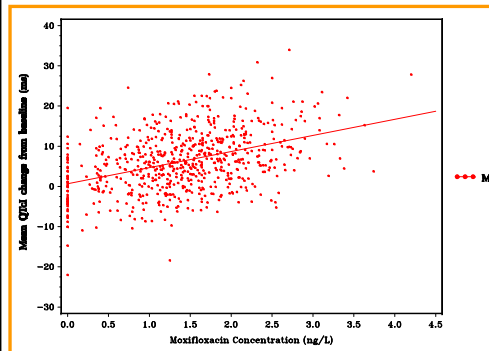


Figure 1 QTcI change from baseline against plasma concentration for moxifloxacin 400 mg

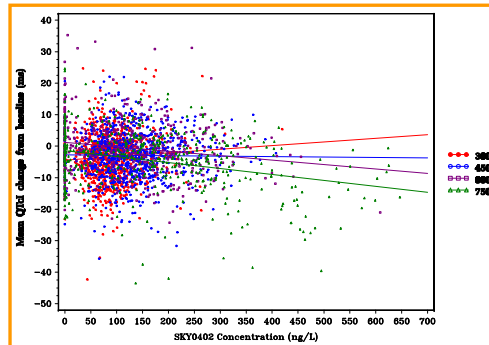


Figure 2 QTcI change from baseline against plasma concentration for SKY0402 300 mg, SKY0402 450 mg, SKY0402 600 mg and SKY0402 750 mg

An increase in moxifloxacin plasma concentration was associated with a moderate increase in QTcI (Figure 1). A change of approximately 5 msec per 1 ng/L corresponding to approximately a 20 msec increase in QTcI change at the higher end of the moxifloxacin range (0-4 ng/L) was observed.

Increasing SKY0402 plasma concentration resulted in a slight decrease in QTcI (Figure 2).

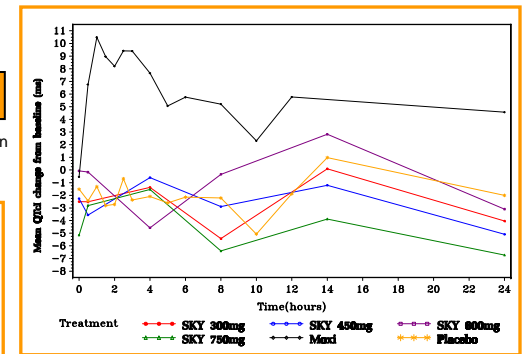


Figure 3 QTcI change from baseline against time for moxifloxacin 400 mg, SKY0402 300 mg, SKY0402 450 mg, SKY0402 600 mg, SKY0402 750 mg and placebo

Conclusions

This thorough QTc study was initially designed to investigate two doses of SKY0402 using 400mg moxifloxacin as a positive control. An exploratory arm was added to investigate higher doses of SKY0402 when plasma levels were found to be lower than anticipated.

All four doses of SKY0402 did not have any clinically significant effect on QTc, a slight shortening of the QTc interval was observed (more than placebo) which appears to be dose dependent. The clinical significance of shortening of the QTc interval in the region of 5 msec is not known but currently considered to be of no clinical concern [6]. QTc shortening has also been described in published data for other medicines [5].

This study shows that bupivacaine given subcutaneously as a new extended release formulation SKY0402 in doses of up to 750 mg does not prolong the QT interval and raises no cardiac concerns.

References

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