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SAFETY AND TOLERABILITY OF PROPIVERINE HYDROCHLORIDE IN PATIENTS WITH SEVERE RENAL IMPAIRMENT (SRI)

Hypothesis / aims of study

The aims of this study were

- to investigate the influence of impaired renal function on the pharmacokinetics of propiverine and its metabolite propiverine-N-oxide
- to characterise the safety and tolerability of 30 mg propiverine in the study population after oral administration under fasting conditions

Study design, materials and methods

A non-randomised, open study with a parallel-group design was performed to investigate pharmacokinetics and tolerability of propiverine after oral administration of a single dose of 30 mg propiverine hydrochloride in male and female subjects with severe renal impairment in comparison with healthy subjects matched by age, BMI and gender.

A total of 24 Caucasian subjects, aged between 18-75 years, with a BMI of 19-31 were enrolled (12 in each group). The groups differed by health state and renal function: **healthy volunteers** were characterized by good state of health and had an estimated creatinine clearance $\geq$ 80ml/min (according to Cockroft-Gault formula); severe **renal impaired patients** were characterized by an estimated creatinine clearance $<$ 30 ml/min.

Safety evaluation: The Prestudy-examination consisted of complete physical examination including medical history and laboratory investigation (blood, urine). The Poststudy-examination consisted of the same examinations with the exception of virology status. AEs were documented and evaluated.

Pharmacokinetic evaluation: The following pharmacokinetic parameters were determined: AUC(0-tlast), AUCtot, AUCexpol, AUCexpol%, C(max), C(last), t(max), t(last), t(1/2), λz, CL, Vd(z), Ae(t_i -t_{i+1}), Ae(0-96) and CL(R). The total body clearance CL and the volume of distribution Vd(z) of propiverine were calculated.

Pharmacodynamic evaluation:

Pharmacodynamic measurement of accommodation distance was performed to assess this pharmacodynamic effect in healthy and renal impaired volunteers. Time points of measurement were set prior to administration of study drug (baseline) as well as 2.5 h, 3 h, 24 h and 48 h after administration.

Statistical methods: Parametric point and interval estimates for the ratio of t(1/2)-, AUC-, C(max)- and CL(R)-values from subjects with severe renal impairment versus subjects with normal renal function were calculated for propiverine and propiverine-N-oxide (t(1/2)2/t(1/2)1, AUC2/AUC1, C(max)2/C(max)1, CL(R)2/ CL(R)1), if applicable. These estimates were analysed after logarithmic data transformation. Prior to the study a pharmacokinetic simulation based on a real existing data set had been performed in order to calculate the theoretical terminal elimination rate constant of propiverine and its primary metabolite which resulted in an increase up to double maximum concentration at steady state. The resulting simulation had shown that the terminal elimination rate constant could increase with a factor of 2.2 for propiverine and 1.9 for propiverine-N-oxide before double maximum concentrations would have been observed in an iterative calculation for steady state conditions.

Results

Safety results:

In general the study drug was well tolerated. During pre-treatment phase four subjects showed AEs (three healthy subjects, one renal impaired). After study drug intake in total eight volunteers showed AEs, which comprised visual disturbance, aerophagia, dry mouth, headache, paraesthesia, dysuria and haematoma. Seven of these occurred in healthy subjects. All AEs during treatment phase were of mild intensity and recovered completely. All changes in clinical laboratory parameters were judged as clinically not relevant and no

tendencies of distinct parameters could be seen. No clinically relevant changes of vital signs and ECG parameters were determined.

Pharmacokinetic results:

Mean pharmacokinetic parameters of propiverine are given in Tables below:

Pharmacokinetic parameters of propiverine

		Healthy subjects				Renal impaired patients			
parameter	unit	mean	median	min	max	mean	median	min	max
C(max)	ng/ml	130.0	126.5	95.0	200.0	155.5	170.0	52.0	318.0
t(max)	h	1.9	2.0	1.5	2.5	1.8	1.5	1.0	3.0
AUC(0-t_{last})	h*ng/ml	1245	1413	561.6	2452	2260	3072	291.5	7624
t(1/2)	h	20.8	19.1	5.7	45.1	32.4	23.5	5.3	93.9
MRT	h	26.4	22.7	8.6	54.3	42.2	32.4	8.5	115.5
Clearance	ml/min	342.2	282.2	157.5	760.5	275.2	122.2	47.7	1303
Vd (z)	l	482.9	430.8	317.6	784.8	428.3	317.6	162.5	863.0

Mean major pharmacokinetic parameters of propiverine N-oxide are given in Tables below:

Pharmacokinetic parameters of propiverine N-oxide

		Healthy subjects				Renal impaired patients			
parameter	unit	mean	median	min	max	mean	median	min	max
C(max)	ng/ml	1080	1097	735	1563	765	758	484	1459
t(max)	h	1.6	1.5	1.0	2.5	2.0	1.8	1.0	3.0
AUC(0-t_{last})	h*ng/ml	8734	8172	5879	17094	13326	14281	3949	25634
t(1/2)	h	18.7	11.3	7.6	78.4	27.3	25.9	11.8	57.5
MRT	h	16.6	11.9	8.0	52.6	33.9	30.0	14.2	62.5

Pharmacodynamic results:

The course of the individual curves determined for accomodation distance showed a slight decrease in both groups after 2.5 and 3 hours.

Statistical results:

The ratio (group 2 vs. group 1) of apparent elimination half life of propiverine was 1.56 which did not exceed the pre-defined limit of 2.2. The ratio of the metabolite propiverine N-oxide was 1.46, so that the predefined limit of 1.9 was not exceeded, too.

Interpretation of results

The results confirmed that renal impairment does not alter elimination and metabolism of propiverine to an extent that warrants dosage adjustment. Analysis showed a high variability of pharmacokinetic parameters. However, in the case of t(1/2) - variability a closer look to distinct volunteers is needed. Only slight differences in t(1/2) - values could be observed between healthy subjects and patients for nearly 75% of the volunteers. Moreover, values of creatinine clearance did not correlate to apparent elimination half-lives and values of renal clearance for propiverine and propiverine N-oxide.

Higher C(max) values of propiverine in renal impaired volunteers are indicating a diminished metabolism in renal insufficient patients. In general, observed differences in pharmacokinetic parameters therefore seem to be due mainly to the multimorbidic appearance of renal insufficient patients. Hence, influence of renal insufficiency on drug elimination seems to be less important as shown by determination of apparent elimination half-lives.

Concluding message

Thus, from a concluding therapeutic point of view, no dose adjustment of propiverine hydrochloride needs to be recommended for severe renal impaired patients.