Translational Research with Dexmedetomidine (DM) for the Treatment of Agitation from Healthy Volunteers to Two Patient groups: Those with Schizophrenia or with Probable Senile Dementia of the Alzheimer's Type (SDAT)

Sheldon Preskorn[1], Rishi Kakar[2], Hrishikesh Kumar[3], Sameer Sharma[†], Vince O'Neill[†], Robert Risinger[†], Frank Yocca[†]

[1]Kansas University School of Medicine, [2]Southern Winds Hospital, Hialeah, Florida, [3]Institute of Neurosciences, Kolkata ,[†]Bioxcel Therapeutics, New Haven, Connecticut

BACKGROUND

DM is a highly selective alpha-2 adrenergic agonist currently marketed for intravenous (IV) administration to sedate/anesthetize patients prior to and/or during surgical procedures and to sedate intubated and mechanically ventilated patients. Given the role of the central adrenergic system in arousal, DM may be useful for the treatment of agitation in patients with various neuropsychiatric disorders including senile dementia of the Alzheimer's Type (SDAT) and schizophrenia.

OBJECTIVE

Present the stepwise transition from preclinical studies to studies in healthy human volunteers to the study of the efficacy of intravenous (IV) dexmedetomidine (DM) in treating agitation in patients with

- Schizophrenia
- Probable Senile Dementia Alzheimer's Type (SDAT) patients

MATERIALS & METHODS

Three identically designed, double-blind, placebo-controlled, randomized studies were conducted with the IV formulation of DM in
(a) Middle-aged to elderly healthy volunteers (HV); Cohort I & II
(b) Agitated patients with schizophrenia
(c) Agitated patients with Senile Dementia of the Alzheimer's Type (SDAT).

The numbers of participant in each study were 12-14 & 4-6 subjects treated with DM and placebo, respectively.

Each study in humans employed a step-wise ascending IV dose titration to determine the dose in healthy volunteers and subjects with Schizophrenia or SDAT which produced the desired efficacy without decreasing blood pressure and/or heart rate. This approach permitted each volunteer to serve as their own control in addition to a double-blind, random assignment placebo control and thus permitted the efficient determination of the variability in the dose needed to achieve the desired effect in individual subjects.

Predosing with DM at 0.5 -1.5 mcg/kg iv in a rat intruder model was effective in preventing the development of agitation. Based on this result, the first studies in humans were conducting in healthy volunteers in which DM was administered IV with a starting dose of 0.1 mcg/kg/hour and the dose was increased by 0.1mcg/kg/hour every 30 minutes up to a maximum dose of 0.6 mcg/kg/hour or until predetermined endpoints were met either for efficacy or reduction in BP or HR to predetermined thresholds.

Continuous assessment was made for the level of arousal and/ or improvement in agitation & cardiac parameters. Blood samples were collected before/after dosing every 15 minutes for the determination of DM concentration in blood to correlate PK and PD effects. In case of HV, mild sedation was taken as the surrogate for efficacy and measured using the Richmond Agitation Sedation Scale (RASS). In the 1st cohort, we used a target of arousable sedation (i.e., RASS = -2). In the 2nd cohort, we used drowsiness (RASS = -1).

- In Schizophrenia patients, the PANSS excitatory component (PEC) scale was used as a marker for efficacy as well as RASS.
- In SDAT patients, the RASS was used as the marker for efficacy . Statistics were descriptive and correlational in terms of pharmacodynamic and pharmacokinetic relationships.

RESULTS

	Healthy Volunteers Cohort 1	Healthy Volunteers Cohort 2	Alzheimer's Study	Schizophrenia Study (RASS) (PEC)
Dose range of Dex (efficacious)	0.3-0.5mcg/kg/hr	0.3-0.4 mcg/kg/hr	0.2-0.5 mcg/kg/hr	0.2 - 0.4mcg/kg/hr
Total dose	21 - 79mcg	12 mcg - 33 mcg	7 mcg - 34 mcg	5 mcg - 32 mcg
Efficacy (Primary/secondary end point)	6/6 RASS-1	5/6 RASS-1	7/10 RASS-1	9/10 RASS-1 9/10 PEC (Score Below 7)
Plasma Conc. achieved at Efficacy dose	114-632 pg/ml	119-363 pg/ml	102-334 pg/ml	22-406 pg/ml
Hemodynamic effects	In three patients systolic BP fall >20mmHg	One patient (001) having left side headache. All hemodynamic parameters remains in normal limit	All hemodynamic parameters remains with in the normal limit	One patient (004) having headache. Desired RASS achieved. All hemodynamic parameters remains in normal limit

SUMMARISED DATA FOR THE EFFECT OF CONTINUOUS IV DM INFUSION IN HV, SCHIZOPHRENIA AND SDAT PATIENTS

Subject Code*	Gender	Age (Yrs.)	Weight (Kg)	IV infusion rate at which desired effect/ stopping criteria achieved (mcg/kg/hr)	Cumulative dose (lowest to highest In mcg)	Plasma conc. (pg/ml)	Endpoint	Plasma conc at RS (pg/ml)	Time needed to resolve (mins)
1201	Female	56	80.7	0.3	12	118.5	RASS -1	41.8	117
1101		73	51.5	0.4	18.4	114.42	BP & HR > RASS -1	75.35	106
1106		58	80.6	0.3	17.7	103.65	RASS - 2	44.2	135
1108		57	70.1	0.3	19.7	182.73	BP & HR > RASS -1	75.46	89
1202		56	60.1	0.4	19.1	246.85	BP > RASS -1	87.94	75
1205		60	112.4	0.4	23.4	342.37	RASS -1 > BP	120.37	59
1207	Male	59	95.8	0.4	28.6	362.62	RASS -1 & no BP/HR	72.02	115
1105		75	66.8	0.3	31.7	263.2	BP & HR > RASS -1	52.86	148
1208		56	81.9	0.4	33.4	270.22	RASS -1 > HR	91.92	89
1104		58	88.7	0.4	41.7	406.27	BP & HR > RASS -1	160.41	> 60*
1103		56	78.9	0.5	56.5	631.64	BP & HR > RASS -1	169.24	102
1204		66	72.7	0.4	25.4**	320.51	No RASS or BP/HR	187.39	NA**

Table 1 : Effect of Continuous IV DM Infusion in Healthy Volunteers:
The table above summarizes the effect of continuous IV infusion of the DM to endpoint in healthy elderly volunteers. Gender specific effect on responsiveness to DM was observed in the study with females being more sensitive than males. The participants in cohort 1 were designated by number 11-- and those in cohort 2 by numbers 12--.Time needed to resolve refers to the time from the cessation of the infusion to the resolution of the pharmacodynamic effect of the drug on either arousal or blood pressure and heart rate. * time not captured by site; **did not have an effect from the infusion; Effect evident in 11/12 subjects.

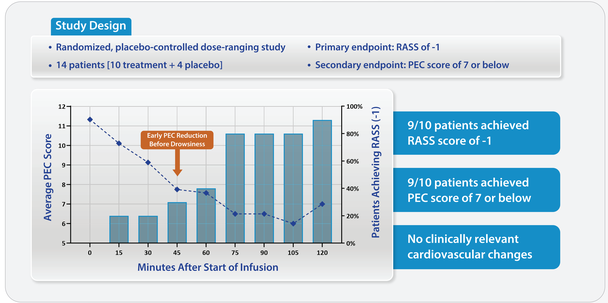

Figure 1: Effect of an IV DM infusion in agitated patients with Schizophrenia using a continuous ascending dose titration to endpoint approach
The figure above summarizes the effect of DM on agitated patients with schizophrenia. The duration of the infusion was continued until either efficacy was achieved (i.e., RASS-1 and reduction in PEC) or the stopping criteria was achieved in terms of BP and HR. Efficacy was obtained in 9/10 patients with no significant hemodynamic effects. The plasma conc. needed for efficacy ranged from 22 to 406 pg/ml and the dose dose ranged from 5mcg to 32mcg.

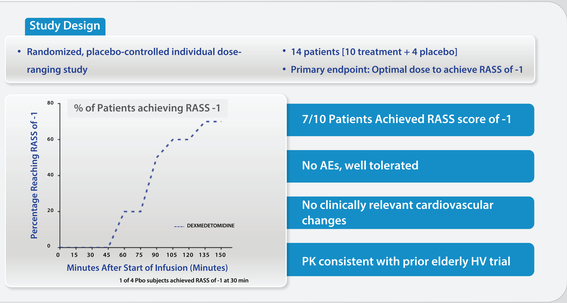

Figure 2: Effect of an IV DM infusion in agitated patients with SDAT using a continuous ascending dose titration to endpoint approach
The figure above summarizes the effect of DM in agitated patients with SDAT. The duration of the infusion was continued until either RASS -1 was achieved or predetermined stopping criteria BP and HR occurred. Efficacy obtained in 7/10 patients with no significant hemodynamic effects. The plasma conc. needed for efficacy ranged 102-334 pg/ml and the dose ranged from 7mcg to 34mcg.

SUMMARY OF RESULTS

- Treatment with DM was capable of producing a light sedation in all subjects (RASS = -1) in HV group. Gender affected drug responsiveness with males requiring twice the dose of DM compared to females.
- In agitated patients with SDAT, DM was capable of achieving the RASS -1 in 7/10 patients with no significant hemodynamic effects at plasma conc. Ranging from 102 to 334 pg/ml and a dose ranging from 7mcg to 34mcg.
- In agitated patients with Schizophrenia, patients DM was able to achieve RASS-1/PEC<7 in 9/10 patients with no significant hemodynamic effects at plasma conc. ranging from 22 to 406 pg/ml and a dose ranging from 5mcg to 32mcg.
- There was an approximately 4-fold variability in the dose and plasma concentration needed to produce these effects in all three groups. The effective dose range was the same across all three groups.

CONCLUSIONS

This study demonstrated the efficiency of an adaptive, translational design to early phase CNS drug development and is directly relevant to three topics of interest to the Society: Translational Research into Clinical Practice, Patient-focused Drug Development, and Genomics. Using this information, a sublingual film formulation has been developed for further studies.

BIBLIOGRAPHY

- Precedex FDA label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021038s027lbl.pdf)
- Sztajzel J, Jung M, Bayes de Luna A: Reproducibility and Gender-Related Differences of Heart Rate Variability during All-Day Activity in Young Men and Women. Ann Noninvasive Electrocardiol. 2008 Jul;13(3):270-7.
- Raskind MA, Millard SP, Petrie EC, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Hill J, Daniels C, Hendrickson R, Peskind ER. Higher Pretreatment Blood Pressure Is Associated With Greater Posttraumatic Stress Disorder Symptom Reduction in Soldiers Treated With Prazosin. Biol Psychiatry. 2016 Nov 15;80(10):736-742.
- Carrasco G, Baeza N, Cabré L, et al. Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial. Crit Care Med. 2016 Jul;44(7):1295-306.
- Aalten P, de VugtME, Jaspers N, et al. The course of neuropsychiatric symptoms in dementia. Int J Geriatr Psychiatry. 2005;20(6):523-530.

CONTACT

FRANK YOCCA (CSO) , *BioXcel Therapeutics*
12th Floor, 555 long Wharf Drive, New Haven, CT, USA
@ fyocca@ bioxceltherapeutics.com 302 299 3653