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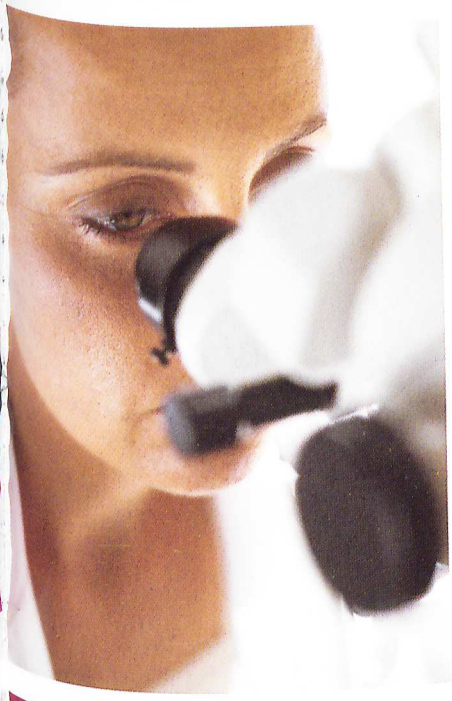

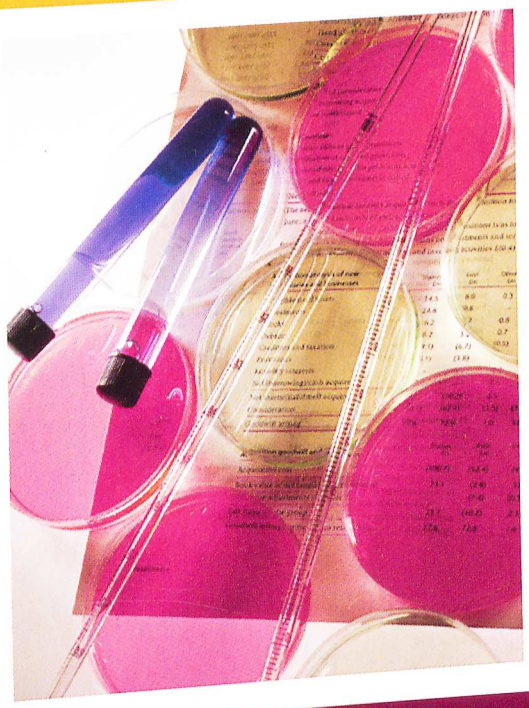

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RESULTS: Mean pharmacokinetic results are reported below:

	AUC (ng*min/mL)			Cmax (ng/mL)			Tmax (min)		
Group (n=5)	Mean	S.D.	CV%	Mean	S.D.	CV%	Mean (min-max)	S.D.	CV%
Naratriptan Alone	62851	17299	28	1052	303	29	27 (15-30)	7	25
Naratriptan/ Carrier A	73568	9377	13	1315	490	37	13* (5-15)	5	34
Naratriptan/ Carrier B	57587	18231	32	940	320	34	9* (5-15)	5	61

* Naratriptan and carrier combination versus control (Naratriptan alone), p=0.02

CONCLUSION: Peak naratriptan concentrations following drug-carrier combination were reached significantly earlier than when naratriptan was administered alone. The extent of absorption, measured as AUC and Cmax, was not substantially affected by the administration of the combination.

PI-74

ASSESSMENT OF THE DOSE PROPORTIONALITY OF PALIPERIDONE PALMITATE 25, 50, 100 AND 150 MG EQ., A NEW LONG-ACTING INJECTABLE ANTIPSYCHOTIC FOLLOWING ADMINISTRATION IN THE DELTOID OR GLUTEAL MUSCLES. A. Cleton,[1] S. Rossenu,[1] D. Hough,[2] H. Crauwels,[1] J. Berwaerts,[2] S. Gopal,[2] A. Vandebosch,[1] C. Rosso Fernandez[3]; [1]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium, [2]Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ, [3]Clinical Trial Unit, University Hospital of Bellvitge, Barcelona, Spain

BACKGROUND: Study evaluated dose proportionality of paliperidone palmitate injections administered in either gluteal or deltoid muscle.

METHODS: A single-dose, open-label, parallel-group study randomized 201 schizophrenia subjects (safety set) into eight treatment groups: paliperidone palmitate 25 (n=48), 50 (n=50), 100 (n=51) or 150 (n=52) mg eq. injected into deltoid or gluteal muscle. Paliperidone dose proportionality was assessed by a linear regression model, for each injection site, with log-transformed dose-normalized AUC_∞ and C_{max} as dependent variables and log-transformed dose as predictor, respectively. C_{max} and AUC_∞ ratios of enantiomers [R078543(+)/R078544(-)] were documented.

RESULTS: AUC_∞ slopes were not significantly different from zero for deltoid (slope -0.06;p=0.36) and gluteal injections (slope -0.02;p=0.76) indicating dose proportional increase in AUC_∞. T_{max} was comparable for doses but slightly earlier for deltoid (13-14d) vs gluteal injections (13-17d). Median C_{max} (range 5.1-11.0ng/mL) was higher with deltoid vs gluteal injections except for 100mg eq. dose. C_{max} slopes were significantly different from zero for deltoid (slope -0.22, p=0.0062) and gluteal (slope -0.31;p<0.0001) injections, indicating a less than proportional increase in C_{max} with dose. Median (+)/(-) C_{max} and AUC_∞ ratios were ~1.7. After a single dose of paliperidone palmitate, subjects received concomitant oral antipsychotics. Treatment-emergent AEs (TEAEs) included tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%), weight gain (5%). Only 2% of subjects discontinued due to TEAEs.

CONCLUSION: Data indicate AUC_∞ increased proportionally with increasing paliperidone palmitate doses (25-150mg eq.), regardless of gluteal or deltoid injection. C_{max} was less than dose proportional for doses >50mg eq. Overall, deltoid injection was associated with a higher C_{max} (except for 100mg eq.) and slightly earlier t_{max} vs gluteal injection.

PI-75

EVALUATION OF THE PHARMACOKINETIC PROFILE OF GLUTEAL VERSUS DELTOID INTRAMUSCULAR INJECTIONS OF PALIPERIDONE PALMITATE 100 MG EQUIVALENT IN PATIENTS WITH SCHIZOPHRENIA. A. Cleton,[1] S. Rossenu,[1] D. Hough,[2] H. Crauwels,[1] A. Vandebosch,[1] J. Berwaerts,[2] M. Eerdekens,[1] I. Francetic[3]; [1]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium, [2]Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ, [3]Institute of Clinical Pharmacology, Clinical Hospital Centre, Zagreb, Croatia

BACKGROUND: The aim of this study was to compare the PK profile of paliperidone palmitate 100 mg eq. administered into the deltoid (n=24) or gluteal muscle (n=25).

METHODS: In this multiple-dose, open-label, parallel-group study, patients with schizophrenia were randomized to receive 4 consecutive injections (Days 1, 8, 36 and 64).

RESULTS: The median C_{max} was higher in deltoid vs. gluteal muscle after the 2nd (31.3 vs. 24.1ng/mL) and 4th (23.7 vs. 22.3ng/mL) injections. After 4 injections, the median fluctuation index (FI) was higher (71.9 vs. 56.2%), with a larger intersubject variability for deltoid vs. gluteal injection. Median T_{max} was similar between injection sites after the 2nd (10 vs. 10 days) and 4th injections (5 vs. 6.5 days). The median concentration-time profile was higher following deltoid injection. After 4 injections, median AUC_∞ was similar for both injection sites; C_{max} and AUC_τ for paliperidone were 30% (90%CI=100.56-168.93) and 20% (90%CI=93.09-154.69) higher in deltoid vs. gluteal muscle, respectively. Increased median predose plasma concentrations on Days 8, 36 and 64 suggested subjects were not completely at steady state after 4 injections. Most commonly reported adverse events (combined injection sites) were orthostatic hypotension (24%), hypotension (14%), diastolic hypertension (12%) and injection site pain (14%). Four patients discontinued due to psychosis. Paliperidone palmitate was well tolerated, with a mean injection site pain VAS score of 3.3 for gluteal vs. 10.8 for deltoid muscle (Day 1, 8 hours after injection).

CONCLUSION: Paliperidone palmitate 100 mg eq., had an increased AUC_τ, higher C_{max} and greater FI when injected into the deltoid vs. gluteal muscle, although similar T_{max} was noted, for both injection sites. Paliperidone palmitate 100 mg eq. was well tolerated.

PI-76

RECIRCULATORY PHARMACOKINETIC MODEL OF FENTANYL AEROSOL IN VOLUNTEERS. M. J. Avram, PhD,[1] T. K. Henthorn, MD,[2] D. A. Spyker, PhD, MD,[3] J. V. Cassella, PhD[3]; [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]University of Colorado Health Sciences Center, Denver, CO, [3]Alexza Pharmaceuticals, Inc, Palo Alto, CA

BACKGROUND/AIMS: A thermally-generated aerosol (TGA) system can deliver pure drug reliably to the alveoli, resulting in rapid systemic drug absorption.[1] This study determined the pharmacokinetics (PK) of fentanyl from the moment of administration as a TGA and as a rapid intravenous (IV) infusion to volunteers and absolute TGA bioavailability.

METHODS: Fentanyl disposition was determined twice in each of 10 healthy volunteers (5 males, 5 females, mean ± SD age 25.3 ± 4.0 yr and weight 77.7 ± 7.4 kg) in this IRB-approved 2-period crossover study. Studies were conducted after a 5 s IV (25 µg) infusion and after a TGA (25 µg coated dose) via Staccato® Fentanyl for Inhalation, Alexza Pharmaceuticals, Palo Alto, CA, delivered in a single breath. Twenty-five arterial blood samples were collected from 15 sec to 8 h after drug administration. Plasma fentanyl concentrations were measured by liquid chromatography-tandem mass spectrometry. IV and TGA PK were characterized simultaneously by a recirculatory PK model.[2]

RESULTS: TGA fentanyl administration produced plasma arterial drug concentrations similar to those produced by rapid IV infusion. The good simultaneous fit of the recirculatory model to arterial