Comparative PK-PD Study On A Long Acting PLGA-based Microsphere of A Novel Antipsychotic and Oral Administration of Free Drug

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ABSTRACT SUMMARY
A long acting PLGA-based microsphere of a novel antipsychotic, isoperidone (Iso) was revealed in previous study, which showed a two-week quazi-zero-order release on beagle dogs. This research had further studied on the PK-PD relationship of isoperidone microsphere and compared with oral administration of free drug. Results had indicated a strong correlation between drug plasma level and antipsychotic effect. A stable drug plasma concentration was observed both intraday and interday from 8 d to 22 d after a single injection of isoperidone microsphere on mice, which present a sustained suppressing effect on the schizophrenia mice model in parallel. Comparatively, the oral administration group was much dose dependant, the pharmacologic effect faded away rapidly along with the drop of drug plasma level after 3 days’ continuous daily dosing.

INTRODUCTION
Schizophrenia is a chronic psychosis which required long term treatment and has a risk of relapse caused by medication interruption, which is often associated with ordinary daily treatment, the high dose and fluctuate drug plasma concentration of which may also lead to another serious side effect of tardive dyskinesia. In light of this, a long acting formulation with the lowest effective dose could favor patients a lot in both preventing recurrence of psychosis and lower the risk of developing tardive dyskinesia.

Isoperidone is a novel atypical antipsychotic proved to be high effective with a comparative more safety profile. The aim to design PLGA-based isoperidone microsphere is to present a stable and effective plasma drug level in vivo with a sustained antipsychotic effect, which may provide as an optimized alternative in clinic.

EXPERIMENTAL METHODS
Isoperidone microspheres of 30% theoretical drug loading were prepared by o/w solvent evaporation method. PLGA (75:25 7E, MW 113,000 Da) was used as the loading material, isoperidone/PLGA/dichloromethane oil phase was prepared and emulsified in 0.5% PVA solution, formed microspheres were further solidified, collected, washed, and lyophilized. The particle size and surface morphology were also studied.

The pharmacokinetic and pharmacodynamic studies were perform on two parallel groups with the same formulation and the same experiment time point. The same single dose of 52.32 mg/kg of isoperidone microspheres were administered subcutaneously on the back of mice for each pharmacokinetic blood sampling time point (n=6) and pharmacologic effect observation (n=10). A repeated daily dose of 4.67 mg/kg of free isoperidone were administered intragastric to mice for 3 days of pharmacokinetic study group (n=6 at each time point) and pharmacological evaluation group (n=10). Schizophrenic model was established through MK-801 (0.6 mg/kg) induced stereotypy activities on male mice (Kunming strain, body weight 20 ± 2 g). Suppressing effects were scored according to 5 levels of inhibition degrees: 0 - absent, 1 - equivocal activities, 2 - present activities, 3 - intense activities, 4 - intense and continuous stereotypy activities.

RESULTS AND DISCUSSION
Integral microspheres of smooth surface (Fig.1) were achieved with an average particle size of 80.35 µm and 26.67% actual drug loading. After single injection of the designed formulation of isoperidone microsphere, a sustained drug release from 8d to 22d was observed in vivo accompanied with significant...
suppressing effect \((p<0.01\) based on student’s T-test\) on the established schizophrenic mice model (Fig.2). The measured plasma drug concentration in the initial, middle, end of drug release had exerted a close link with the pharmacologic response, which indicated a strong correlation in-between.

The PK-PD relationships within day of 8d, 12d and 22d after a single injection of isoperidone microsphere (Fig.3) were also evaluated in comparison with the oral administration group (Fig.4) at the corresponding interday time point of 0.5h, 3h, 8h, 24h. The microsphere group showed a lower plasma drug level on 8d and no observed suppressing effect before 2h within 8d, however, through the middle and end of the drug release period, it had maintained a stable and effective plasma drug level accompanied by a significant suppressing effect \((p<0.01)\) till the end of 22d. Comparatively, the oral administration group were not able to maintain a steady plasma drug level within day to keep a continuous suppressing effect post 3 days daily dosing.

**CONCLUSION**

The designed PLGA-based isoperidone microsphere possesses a good potential to provide a sustained and stable plasma drug concentration in vivo through two-week drug release period to maintain a continuous antipsychotic effect.

**REFERENCES**