Problem set 2020-2

March 8, 2020

Due March 25, 2019

1. (15)

You are leading the drug delivery effort for a team working on new atypical antipsychotic. These drug candidates are tertiary amines of a more complex chemical structure than risperidone or olanzapine. The compounds were discovered and isolated by a laboratory at Berkley California. The team of researchers you collaborate with (here in Cambridge) has acquired the patents for these compounds and is now working on the most active analogs of this chemical series.

There are four lead compounds that are very active. They have been synthesized, in very small quantities, and all have good activity against the D2 and 5HT2A receptors. The freebase forms of these analogs have been found to have low solubility in water at 25oC. The properties of these four analogs are shown in Table 2.1. **Determine the solubility of all four compounds at pH=5, PH=6 and PH=7**. The pharmacologist on your team would like to be able to test the four compounds against each other and needs a buffered solution where all the leads are soluble in the same buffer and pH.

- **Is there a pH where all the of the compounds are water soluble at >10 mg/mL (25oC)**

Table 2.1. Properties of lead drug candidates.

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound** | **MW**  **(Daltons)** | **Free Base Water Solubility (g/mL)** | **pKa**  **Amine** |
| D2 | 422 | 11.2 | 8.6 |
| D5 | 394 | 4.6 | 9.1 |
| D6 | 388 | 2.9 | 9.3 |
| D12 | 465 | 5.8 | 8.6 |

1. (15)

The clinical compound was selected (from the four lead compounds in Table 2.1) on the basis of activity and metabolic stability. A bolus IV pharmacokinetic study was done in young healthy male volunteers (n=8, from MIT) at a **2 mg dose** to evaluate the half-life and volume of distribution of the clinical compound. The mean pharmacokinetic plasma concentrations are shown in Table 2.2.

**-Determine the volume of distribution, elimination rate constant and half-life of the drug, assuming a one compartment model with first order elimination.**

Table 2.2 Mean pharmacokinetic plasma levels from eight healthy volunteers, 2 mg IV bolus dose.

|  |  |
| --- | --- |
| Hours post bolus infusion of 2 mg | Plasma concentration (ng/mL) |
|  |  |
| 1 | 9.9 |
| 2 | 9.6 |
| 4 | 8.9 |
| 8 | 7.8 |
| 24 | 5.4 |
| 48 | 2.4 |
| 72 | 1.2 |
| 96 | 0.6 |
| 120 | 0.2 |

1. (25)

All of the lead analogs have good oral bioavailability in animal models, but the decision is made to make the focus for development a **Long Acting Injectable Antipsychotic**. An oral product will be developed in parallel. The chemistry group believes that making a pro-drug ester is not feasible. So, you must develop an **injectable PLGA depot, with a target duration of release of 2 weeks (dosing every 2 weeks), with a minimal lag time and minimal burst.**

You have designed an experiment to evaluative different PLGA compositions and molecular weights. Your team used a small scale emulsion process to produce batches of each of the formulations listed in Table 2.3a. Each formulation was evaluated for **in vitro burst in 37oC in phosphate buffer (pH 7).** The data from the in vitro release experiment are listed in Table 2.3a., where the **24 hour time point is considered burst release.**

The in vivo release of these six different formulations are shown in Table 2.3a, the pharmacokinetics were done in Sprague Dawley rats. Table 2.3b is the in vivo release pharmacokinetic data for rats.

**-Using the data in Tables 2.3b determine the area under the curve (AUC) from the start of the experiment (t=0) to the end of sampling (t=day 35) for each formulation.**

**-Compare the ratio of AUC for each formulation to Formulation D. Which formulations have low relative areas under the curve and why?**

**-Considering that you want to minimize burst and maintain elevated plasma levels over a two week period of time, which formulation meets those goals.**

**-Determine if there is a correlation between in vitro burst and the day one pharmacokinetic levels observed in rats.**

Table 2.3a. Experimental design of microparticles and in vitro burst results

|  |  |  |  |
| --- | --- | --- | --- |
| **Formulation** | **PLGA**  **Lactide to Glycolide mole ratio** | **Molecular weight**  **(Daltons)** | **In vitro 24 hour release %** |
| A | 85:15 | 175,000 | 3 |
| B | 85:15 | 50,000 | 5 |
| C | 75:25 | 85,000 | 4 |
| D | 75:25 | 15,000 | 12 |
| E | 65:35 | 45,000 | 8 |
| F | 50:50 | 24,000 | 15 |

Table 2.3b. Plasma concentration (ng/mL) in Sprague Dawley rats, IM injection of

0.5 mg/kg of LAI, six different microsphere formulations

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Days | Formulation A | Formulation B | Formulation C | Formulation D | Formulation E | Formulation F |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 3.2 | 2.7 | 1.8 | 10.6 | 7.2 | 18.6 |
| 3 | 1.6 | 1.9 | 2.0 | 1.5 | 25.3 | 32.3 |
| 7 | 1.8 | 2.6 | 2.9 | 13.5 | 26.3 | 21.6 |
| 14 | 1.3 | 2.8 | 12.5 | 19.6 | 5.6 | 4.6 |
| 21 | 1.5 | 3.6 | 11.2 | 6.2 | 2.1 | 1.1 |
| 28 | 1.8 | 5.8 | 13.5 | 2.0 | 1.3 | 0.3 |
| 35 | 2.2 | 3.9 | 2.6 | 1.1 | 0.3 | 0.1 |

4. (25)

The team thinks that determining the dopamine **D2 receptor occupancy as a function of plasma concentration** is important to the development of a LAI product by establishing plasma concentration targets. A study was designed where 14 male patients with schizophrenia were evaluated for D2 occupancy using positron emission spectroscopy. The drug was **administered each day by IV infusion for six consecutive days, over a range of doses**. Both **plasma concentration and D2 receptor occupancy were measured at the end of the sixth day**. The results for the 14 male patients are shown in Table 2.4

**-Assume that the response (D2 receptor occupancy) follows an Emax model with the baseline being 0% occupancy and that the maximum value for D2 occupancy is 100%**

**-Assume that the slope factor is one, which from the literature is consistent with other atypical antipsychotics. Determine the EC50 value in ng/mL.**

**-Graph a complete %D2 occupancy vs. plasma concentration curve for both the observed and calculated points**

**-There is evidence that below 60 to 65% D2 occupancy there is inadequate activity and above 80% there are significant side effects. However, the data from this study indicated that this compound does not produce adverse events even at 87% occupancy. What plasma concentration range will you target for your LAI product to achieve 65% to 85% D2 occupancy.**

Table 2.4. Mean D2 occupancy and plasma levels for patients at end of day 6 infusion

|  |  |  |
| --- | --- | --- |
| Patient | Steady state plasma Cp(ng/mL) | D2 receptor occupancy % |
| 1 | 1.2 | 25 |
| 2 | 1.8 | 44 |
| 3 | 2.5 | 58 |
| 4 | 3 | 60 |
| 5 | 3.9 | 68 |
| 6 | 4.5 | 68 |
| 7 | 4.9 | 67 |
| 8 | 5.6 | 72 |
| 9 | 6.9 | 80 |
| 10 | 7.8 | 79 |
| 11 | 9 | 84 |
| 12 | 10.3 | 77 |
| 13 | 14.2 | 87 |
| 14 | 16.9 | 86 |

1. (20)

The lead microparticle formulation was selected from the results found in problem 2, and was taken on to phase I clinical trials. Six schizophrenic patients were treated with a 35 mg dose of the clinical LAI, where the mean pharmacokinetic profile is shown in Table 2.5.

* **Determine the AUC from 0 to 672 hours and compare the AUC per mg to the IV AUC per mg. What is the estimated bioavailability of 35 mg LAI?**
* **what would you predict the plasma concertation to be one week after the second dose of 35 mg LAI? In other words, first dose of 35 mg LAI at 0 hours, second dose of 35 mg of LAI at 336 hours, and prediction of plasma concentration at 504 hours. What is the estimated percent D2 occupancy at 504 hours?**

Table 2.5 Mean Pharmacokinetic profile for six schizophrenia patients, single dose study with a 35 mg deltoid injection of the LAI product.

|  |  |
| --- | --- |
| **Hours Post Dose** | **Plasma levels**  **(ng/mL)** |
| 24 hours | 0.3 |
| 48 hours | 0.2 |
| 96 hours | 0.3 |
| 168 hours | 8.2 |
| 336 hours | 9.0 |
| 504 hours | 7.5 |
| 672 hours | 0.2 |
| 840 hours | 0.1 |