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Modeling chronic olanzapine exposure using osmotic minipumps: Pharmacological limitations ☆,☆☆

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ABSTRACT

Animal models can face unique challenges in mirroring what occurs in humans. This is the case for antipsychotics in rodents, where these drugs are metabolized much more rapidly. One strategy to address this issue has been the use of osmotic minipumps to ensure continuous antipsychotic exposure over prolonged intervals, which is routinely the case when these same drugs are administered to humans. More recently, it has been identified that with olanzapine this approach may be compromised by oxidative degradation, a process that can be observed within days. Further, in vivo evidence has reported progressive decreases in plasma levels over a 1-month interval. To address this issue in vitro, osmotic minipumps (n = 4), with olanzapine at a concentration resulting in a dose of 7.5 mg/kg/day in vivo, were placed in saline-filled Falcon tubes and immersed in a water bath. Olanzapine concentrations were assessed in the minipumps as well as the surrounding water bath at baseline, 1 h, and days 1, 7, 14, 21, and 28. Minipump results indicated a monophasic exponential decay and a half-life of 14.8 days (95% CI = 13.1–17.1 days). Results from the water bath demonstrated a linear increase in olanzapine up to and including day 21, followed thereafter by a decrease to day 28. It is concluded that administration of olanzapine via osmotic minipump is viable in animal models to mirror what occurs in humans, although the interval should be confined to 2 weeks. As well, strategies in dissolving olanzapine to diminish oxidation are discussed.

1. Introduction

Animal models play an integral role in the field of psychopharmacology (Gilles and Luthringer, 2007; Haney and Spealman, 2008; Kato et al., 2007; Preskorn, 2006; Remington, 2009), and in the case of antipsychotics they have been used routinely to address a number of clinically relevant issues. Our own lab, for example, has used the vacuous chewing movement (VCM) model with rodents as a proxy for tardive dyskinesia (TD), examining risk as a function of individual antipsychotic and route of administration (Turrone et al., 2002a, 2002b, 2003a, 2003b, 2005). More recently, we have again used rodent models to assess antipsychotic-related risk of weight gain/metabolic disturbance (Chintoh et al., 2009, 2008a, 2008b), a topic of considerable concern given the increased risk identified with the newer 'atypical' antipsychotics (Allison and Casey, 2001; Newcomer, 2005, 2007).

In using such models, researchers often opt for chronic administration as this mirrors how these drugs are administered in humans. Antipsychotic dosing is routinely guided by peripheral kinetics and a compound's half-life, with the goal of achieving steady state levels as quickly as possible and maintaining treatment indefinitely in psychotic conditions such as schizophrenia (Ereshefsky et al., 1990; Gitlin et al., 2001; Nayak et al., 1987; Robinson et al., 2004; Simpson et al., 1990; Yasui-Furukori et al., 2002). At least in the case of rodent models though, it has been established that antipsychotic pharmacokinetics differ considerably from what is observed in humans (Kapur et al., 2003, 2000). Specifically, antipsychotics (e.g., olanzapine) are metabolized much more quickly in rodents, meaning that daily administration does not translate to the steady state levels seen in humans with this same approach. For example, in the case of olanzapine its half-life in rats is approximately 2.5 h versus >24 h in humans (Aravagiri et al., 1999; Callaghan et al., 1999; Kassahun et al., 1997). To circumvent this problem, researchers have looked to osmotic minipumps to ensure steady and continuous drug administration over prolonged intervals

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(Kapur et al., 2003); our lab has routinely employed this strategy, administering antipsychotics such as olanzapine and haloperidol over periods as long as one month (Chintoh et al., 2008b; Turrone et al., 2003a, 2005, 2002b).

Specific to olanzapine, it has been pointed out more recently that drug degradation may compromise the prolonged administration permitted with osmotic minipumps (van der Zwaal et al., 2008). A review of four studies that administered olanzapine via osmotic minipump over intervals ranging from 1–4 weeks suggested reductions in plasma levels >50% by 3–4 weeks (Kapur et al., 2003; Li et al., 2005; Seager et al., 2005; Turrone et al., 2005) and the reviewers' own work examining changes for two doses of olanzapine (2.75 and 7.5 mg/kg/d) at 4, 10, and 28 days, indicated a reduction of approximately 50% between days 4 and 10, increasing to >90% by 28 days. Further in vitro work looking at olanzapine in a minipump solution indicated significant degradation (20–30%) within 8 days (van der Zwaal et al., 2008).

A more recent publication from our Centre adds a fifth study to this debate. Olanzapine levels were assessed in male Sprague–Dawley rats (n = 4) following administration of 7.5 mg/kg/day via osmotic minipump (McCormick et al., 2010). Measured plasma levels (±SD) were as follows: day 3, 244 nM (52); day 7, 190 nM (27); day 14, 153 nM (33); day 21, 134 nM (26). While the rate of reduction is not as steep, it amounted to a decrease of 55% between days 3 and 21.

These findings have important implications. Around the world olanzapine quickly became, and it continues to be, one of the most widely used antipsychotics in clinical settings (Chiabrando et al., 2010; Hollingworth et al., 2010; Ponto et al., 2010; Weinbrenner et al., 2009; Yang et al., 2008), and its increased risk of weight gain compared to other atypical antipsychotics other than clozapine (Allison and Casey, 2001; Newcomer, 2005, 2007) has resulted in considerable animal, as well as human, research focused on better understanding the underlying mechanisms of action. As noted, there are a number of published reports based on olanzapine being administered via osmotic minipump over intervals as long as 1 month (Kapur et al., 2003; Li et al., 2005; McCormick et al., 2010; Seager et al., 2005; Turrone et al., 2005), although to date there has been only one report raising concerns about olanzapine's use within this framework (van der Zwaal et al., 2008). Accordingly, the present investigation was designed to provide further data that could guide future studies attempting to model chronic administration of olanzapine through the use of minipumps.

2. Methods

2.1. Ex vivo administration: 4 weeks

To supplement the in vivo findings available, we felt it valuable to examine changes in vitro, hypothesizing that the more controlled environment would provide additional data devoid of the different confounds that can occur in the context of in vivo testing (e.g., delivery, individual pharmacokinetic differences). In line with our previous work (Chintoh et al., 2008b; Turrone et al., 2005), Alzet® osmotic minipumps (Alzet 28-day model 2LM4, 2 mL volume; Durect Corporation, Cupertino, California) were prepared (n = 4) to administer 31.3 mg/mL olanzapine (Toronto Research Chemicals Inc., Toronto, Canada). This is the same concentration as used in our previous in vivo work, and in 250 g animals results in a dose of 7.5 mg/kg/day. For comparison purposes, a control pump (n = 1) was included, which delivered vehicle solution consisting of 2% glacial acetic acid in sterile water, adjusted to pH = 5 using aqueous NaOH.

Pumps were placed in saline-filled, 50 mL Falcon tubes (BD Labware, NJ, USA), which were immersed in a water bath maintained at 37 °C over a 28-day interval. The bath itself was situated in a darkened area with no direct exposure to light. Olanzapine concentrations were determined in the minipump and surrounding saline solution at baseline and at six intervals thereafter: 1 h, days 1, 7, 14, 21 and 28.

Drug levels were determined following the same procedure as described in earlier work from our Centre (Kapur et al., 2003). Drug levels were quantified using a liquid–liquid extraction to prepare the specimen, with the obtained samples separated using liquid chromatography and introduced into the mass spectrometer using electrospray ionization implemented using an HP 1100 LC = DAD-MSD system controlled by HP LC-MSD Chemstation software (Hewlett-Packard, Palo Alto, CA). Olanzapine was quantified with a lower limit of detection of 5 nM and a linearity limit of 800 nM with CV ranging from 2–10%.

3. Results

Olanzapine concentration in the osmotic minipumps (Fig. 1) decreased significantly over time (ANOVA: $F(4,20) = 2133$, $P<0.0001$; Bonferroni multiple comparisons: $P<0.0001$ for all between-day comparisons). The decrease in olanzapine concentration was well described by a monophasic exponential decay function ($r^2 = 0.997$) with a decay constant of 0.0477 d^{-1} (95% CI = 0.041–0.053 d^{-1}) and a half-life of 14.8 d (95% CI = 13.1–17.1 days).

Fig. 2 shows the change in olanzapine concentration over time in the water bath surrounding the minipump. Olanzapine concentration rose significantly from day 1 to day 21 (ANOVA: $F(5,24) = 324$, $P<0.0001$; Bonferroni multiple comparisons: $P<0.001$ for all between-day comparisons), whereas a decrease in olanzapine concentration was seen over the 21–28 day period ($P<0.001$), presumably due to a combination of degradation and insolubility in saline. The concentration of olanzapine increased linearly over the period up to and including day 21 ($r^2 = 0.96$, $F(1, 23) = 586$, $P<0.0001$). Exclusion of the 28 day data point significantly altered the slope of the regression line (ANOVA: $F(3,82) = 16.9$, $P<0.0001$; Bonferroni multiple comparisons, $P<0.001$), whereas the slope was unaffected by further truncation of the data set. Additionally, removal of the 28-day data point increased the r^2 value of the regression line from 0.68 to 0.96, whereas this parameter was relatively insensitive to further truncation (0.98 and 0.97, after removal of 21 and 14 day points).

4. Discussion

With illnesses such as schizophrenia, antipsychotic treatment is characterized by ongoing treatment at steady state levels (Ereshefsky et al., 1990; Gitlin et al., 2001; Nayak et al., 1987; Robinson et al., 2004; Simpson et al., 1990; Yasui-Furukori et al., 2002). In translating this to animal research, at least rodents, osmotic minipumps represent an appealing option given the considerably shorter half-life compared to what is observed in humans (Kapur et al., 2003, 2000).

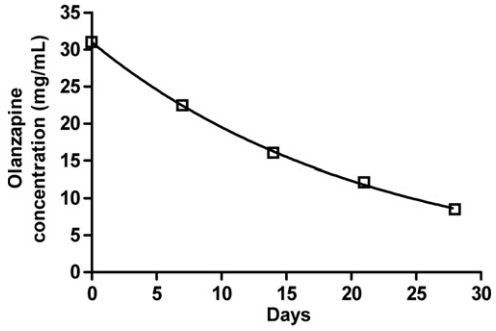

Fig. 1. Olanzapine concentration in the osmotic minupumps over time. The curve represents a mono-phasic exponential fit as described in the results. Note that the error bars (SD) in this figure are fully obscured by the data points.

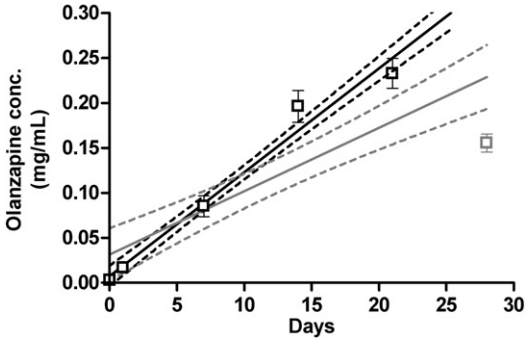

Fig. 2. Change in olanzapine concentration over time in water bath surrounding the osmotic minipumps. The gray curve represents the linear regression of the entire data set, whereas the black curve represents the linear regression obtained when the 28-day data point is excluded. Dotted curves represent the 95% confidence interval of the respective linear regression.

More recently, the use of this strategy with olanzapine has been called into question. One reason to have concerns about olanzapine relates to the physical changes that are observable across time when it is used in this fashion. As reported by van der Zwaal et al. (2008), under these conditions olanzapine displays discoloration, turning a dark green, in keeping with reports that it is readily oxidized (Aravagiri et al., 1999; Callaghan et al., 1999; Kassahun et al., 1997). Degradation oxidation products related to this process have been isolated (Baertschi et al., 2008; Hiriyanna et al., 2008), although the impact of this on various effects of olanzapine remains unclear. In the context of examining olanzapine's risk of weight gain, van der Zwaal et al. (2008) also noted decreases in initial olanzapine-induced weight gain over 4 weeks, leading them to postulate that this could reflect olanzapine's degradation.

The present findings corroborate the concerns raised by van der Zwaal et al. (2008) regarding the use of olanzapine in osmotic minipumps to mirror the condition of chronic, sustained exposure in humans. We add to their body of evidence a more recent in vivo study by McCormick et al. (2010) from our Centre that also confirms marked reduction in olanzapine levels over the course of 4 weeks when administered via osmotic minipump (a reduction of 55% between days 3 and 21). In addition, we demonstrate that despite progressive degradation of olanzapine within the minipump (half-life = 14.8 days) the increase in olanzapine concentration in the saline solution surrounding the minipump can be approximated as linear over a period of 3 weeks, followed by a significant decrease between days 21 and 28 (likely due to degradation of olanzapine in the water surrounding the minipump). Taken together, these data argue against the use of olanzapine administration via osmotic minipump over 1 month, although a 2–3 week design appears a viable option. We also add the caveat that the controlled environment employed here may not precisely mirror what is observed in vivo.

van der Zwaal et al. (2008) correctly call into question previously published studies that have employed olanzapine administration in osmotic minipumps, noting that these data could account for a lack of results or, in the case of an effect, represent an underestimation. This is certainly a distinct possibility, leading us to review our own published data where the design involved 1 month of olanzapine administration via minipump. As noted, we have employed this methodology to examine olanzapine's liability in terms of TD, using VCM's as a proxy (Turrone et al., 2005). Olanzapine 15 mg/kg/day paralleled haloperidol 1 mg/kg/day when both were administered over 2 months via 4-week minipumps, repeated with a second 4-week minipump during month 2 (Turrone et al., 2005). Thus, there was a clear olanzapine effect that was comparable to another antipsychotic, haloperidol in this case, which did not appear to diminish over the course of minipump exposure.

More recently, we have again used minipump-administered olanzapine in rats to better understand its well-known risk for weight gain and related metabolic disturbances in humans (Chintoh et al., 2008b). In this context, we have collected weekly assessments over 1 month of exposure for the following measures: food intake, weight gain, and locomotor activity. Like van der Zwaal et al. (2008), we reported a lack of weight gain with several doses of olanzapine, including 7.5 mg/kg/day (Chintoh et al., 2008b). Their data indicated attenuation of food intake and decreased locomotor activity over the 4-week interval, leading them to postulate that the overall results reflected drug degradation (van der Zwaal et al., 2008). In contrast, our data do not support this hypothesis, in that food intake rose steadily while locomotor activity remained decreased over the course of the 4 weeks (Chintoh et al., 2008b). However, this does not negate the possibility that the olanzapine-induced effects were attenuated, an argument that could also hold true for VCM rates in the aforementioned work (Turrone et al., 2005).

Going forward, what recommendations can be made regarding studies of this sort? van der Zwaal et al. (2008) have recommended that osmotic minipumps not be used in (sub)chronic experiments involving olanzapine. Based on our data, we would recommend that pumps can be used but that their maximum duration be confined to 2 weeks. Of note, there is a more recent report involving chronic olanzapine administration that uses an electric microinfusion pump (iPRECIO®) that permits refilling without re-incision to exchange pumps (Shobo et al., 2011). We also pick up on a point made by these authors, who found that the use of hydrochloric acid, versus acetic acid, seemed to delay drug degradation. One of the co-authors (S Natesan, personal communication), drawing upon the antioxidant properties of cyclodextrin, has employed a combination of hydroxy-propol-β-cyclodextrin 20% w/v and ascorbic acid 5 mg/ml to achieve pH = 6, which provides adequate solubility and stability from oxidation (Nunez-Delicado et al., 1997; Olesen and Linnet, 1998). Using this formulation, plasma olanzapine levels measured 28 days after administration attained an average value of 192 nM for a dose of 10 mg/kg/d (Vernon et al., 2011).

van der Zwaal et al. (2008) also suggest other routes of administration, including depot antipsychotic formulations and external pumps. We concur with the use of depots although those available in long-acting depot form are limited; for the atypicals, the list is presently confined to olanzapine (Frampton, 2010) and risperidone (Harrison and Goa, 2004). It is worth pointing out that the pattern of decreasing olanzapine concentrations over time, in fact, parallels what occurs with use of depot antipsychotics in humans. As routinely administered in humans, depot antipsychotics do not ensure sustained plasma levels over the course of the injection interval (Uchida et al., 2008); for example, D_2 occupancy levels have been reported to decrease in the range of 30% over the 4-week injection interval recommended for haloperidol decanoate (Nyberg et al., 1995) and as much as 24% in the 2-week injection interval recommended for long-acting injectable risperidone (Remington et al., 2006). Our concerns over external pumps relate to the different behavioral measures that are often carried out in the context of these studies and how these might be compromised. Repeated injections (i.p. or s.c.) as well as oral gavage have as well been raised as options; over and above the stress this may incur (van der Zwaal et al., 2008), pharmacokinetics would suggest that even several injections daily would not achieve steady state levels (Kapur et al., 2003, 2000). Oral administration as part of the diet or drinking water, sometimes enhanced by mixing in cookie dough or adding a sweetener, has also been employed (Han et al., 2008; Minet-Ringuet et al., 2006, 2005; Raskind et al., 2007; Weston-Green et al., 2011). However, this strategy faces challenges in terms of variability in volume ingested and timeframe.

In conclusion, drug degradation of olanzapine poses a real challenge in the context of osmotic minipump administration. We suggest that olanzapine administration via this route represents a viable option for (sub)chronic exposure with the caveats that a)

duration be confined to 2 weeks (we highlight that such a strategy most closely parallels what is observed with depot antipsychotic administration in humans), and b) consideration be given to strategies in dissolving olanzapine that diminish the risk of oxidation. Olanzapine levels represent the gold standard in monitoring any changes over time although discoloration is a visible indicator of the oxidative process. Finally, we strongly agree with van der Zwaal and colleagues (2008) that the issue of drug degradation is not specific to olanzapine, and that it is imperative to establish whether compounds being considered for minipump administration are capable of remaining stable in solution at body temperature.

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