Treatment of Adverse Effects of Excessive Phencyclidine Exposure in Rats with a Minimal Dose of Monoclonal Antibody

ELIZABETH M. LAURENZANA, MELINDA G. GUNNELL, W. BROOKS GENTRY, and S. MICHAEL OWENS

Departments of Pharmacology and Toxicology (E.M.L., M.G.G., W.B.G., S.M.O.), and Anesthesiology (W.B.G.), College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas

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ABSTRACT

The range of medical effects and complications resulting from excessive use of drugs of abuse like phencyclidine (PCP) has hindered the development of effective medications. Drug-specific monoclonal antibodies (mAbs) provide an appealing medication approach since they can be selective for the drug, without concern for the sites of action of the drug. The use of mAb medications has been considered impractical because it is commonly believed that very large doses of mAb would be required to treat the adverse medical effects resulting from excessive drug use. In this study, a single dose of an anti-PCP mAb was found to significantly reduce the negative health impact of excessive, prolonged PCP treatment in rats (18 mg/kg/day for 2 weeks). The protective effects were mAb dose-dependent, and mAb doses as low as 1/100th the molar equivalent amount of the PCP body burden were effective at preventing PCP-induced deaths, reducing PCP brain concentrations, and improving the general health status of the animals. They also show that treatment with monoclonal antibody medications can have medically important outcomes without the need to neutralize the entire dose of the offending drug. These results could help establish the feasibility of using carefully designed monoclonal antibody medications to treat drug abuse and addiction, a chronic and re-occurring illness of the central nervous system.

Because of the alluring and addictive properties of drugs of abuse like cocaine, amphetamines, and phencyclidine, users will often increase their doses to the point of serious medical illness and self-destruction. Patients who are using the drugs to this extreme are usually not able to make the rational decisions that are needed to participate in long-term treatment programs (National Institute on Drug Abuse, 1999). Even if they seek treatment, in most cases they are limited to the use of counseling or behavioral modification therapies, because there are no medications to reduce self-administration, craving, or the adverse health effects of these drugs.

Although a few medications are approved for the treatment of nicotine, alcohol, and opiate abuse (Kreek et al., 2002), there are no specific medications for the treatment of medical problems resulting from drugs like cocaine, amphetamines, or PCP. A promising approach is the use of highly specific antidrug monoclonal antibodies (mAbs) or vaccines (Fox et al., 1996; Proksch et al., 2000; Carrera et al., 2001). These protein-based medications are believed to function as pharmacokinetic antagonists, which block or limit the drug from reaching their sites of action in the peripheral and central nervous system. Although there is no evidence to suggest that these treatments reduce drug craving, they do reduce other effects, including drug self-administration and locomotor activity (Carrera et al., 2000, 2001; Hardin et al., 2002).

There are perceived problems with these medications. These problems include the feasibility of giving an adequate dose of mAb to neutralize drug effects, the likelihood of drug abusers surmounting the protective effects of the antibody by simply taking more drug, and the possibility of allergic or autoimmune problems resulting from vaccine or mAb therapy. A common perception is that a mole of antibody binding sites would be needed to neutralize the effects of each mole of drug (Scherrmann et al., 1989). Since serious drug abusers may use gram(s) per day of drug (Burns and Lerner, 1976; Cho, 1990), it appears that the lack of economic and/or medical feasibility would preclude the use of mAbs for the treatment of the high dose self-administration of most drug users. However, the possibility of allergic or autoimmune problems resulting from mAb therapy is usually not a concern if human, humanized, or chimeric antibodies are used for treating humans (Berger et al., 2002).

Our laboratory has developed a high-affinity ($K_d \sim 1.3 \text{nM}$), highly selective mAb for PCP (anti-PCP mAb). Previous studies have shown that a single equimolar dose (1.53 g/kg) of this anti-PCP mAb can provide long-term reductions in PCP brain concentrations during a continuous 1-month PCP infusion.

ABBREVIATIONS: PCP, phencyclidine; mAb, monoclonal antibody; $t_{1/2}$, terminal elimination half-life; ANOVA, analysis of variance.
sion (Proksch et al., 2000). These reductions in PCP brain concentrations occur even when the binding capacity of the anti-PCP mAb should have been saturated by the PCP infusion. Further studies have shown that a single dose of anti-PCP mAb (1.0 g/kg) is effective in reducing the locomotor effects of repeated i.v. PCP doses for up to 2 weeks (Hardin et al., 2002). Although these two studies show that high doses of mAb can protect the brain and substantially reduce locomotor effects, they did not consider the possibility that significantly lower doses of the mAb could also be effective or that the mAb might provide other beneficial effects, like improvements in health status.

In the current study, we tested the hypothesis that lower doses of anti-PCP mAb could effectively reduce and/or reverse the effects of potentially fatal doses of PCP in rats. In addition, we determined whether these low doses of antibody could improve the health status of the animals even in the presence of sustained high doses of PCP. To monitor outcomes, we studied a range of parameters including PCP-induced locomotor activity, changes in body weight, chromodacryorrhea, and PCP pharmacokinetics. Although we were primarily interested in the mAb-induced changes in PCP concentrations in serum and brain, we also studied the testis for at least 5 days before the experiment began, the rats were acclimated to the chambers in which the behavioral experiments were performed. Aliquots were used for the following sections. Immediately after the baseline behavior session, anti-PCP mAb or vehicle was infused via the jugular catheter at a rate of 2 ml/min (8 ml total volume). The doses of anti-PCP mAb ranged from 1.53 g/kg to 5 mg/kg. The highest dose was equivalent to the molar amount of PCP in the body at the time of administration. This mAb dose was calculated using a molecular mass of 150 kDa and corrected for the presence of two binding sites on the mAb molecule. The other anti-PCP mAb doses were equal to 0.3, 0.1, 0.03, 0.01, or 0.003 times the molar equivalent (mol Eq) of PCP. There were four animals per treatment group. We also studied two control groups (i.e., PCP infusion with no antibody treatment), once at the beginning of the experiment and then on a separate occasion 3 months later, at the end of the experiment. An additional control group (n = 4) was studied in which the pump delivered sterile saline only (vehicle for PCP) and the treatment on the day after pump implantation consisted of buffered saline (vehicle for antibody).

**Behavioral Studies.** Behavior experiments were carried out as previously described (Hardin et al., 1998). Briefly, rats were placed in open-top polyethylene chambers (60 × 45 × 40 cm), and spontaneous behavior was recorded by a video camera located above the chambers. Analysis of the behavior videotapes was carried out with Ethovision software (Noldus Information Technology, Inc., Sterling, VA).

**PCP Tissue and Serum Concentrations.** Blood was collected via the inferior vena cava at the time of sacrifice (day 14), and serum was collected after centrifugation. Serum samples (100 μl) were treated with 100 μl of 8 M guanidine hydrochloride and then transferred to a preconditioned 1-ml C18 solid-phase extraction cartridge. The cartridge was centrifuged at ~8000 g for 1 min. The cartridge was then washed with acetonitrile/water (5:95) containing 0.1% trimethylamine. PCP was then eluted from the cartridge with acetonitrile containing 0.1% trimethylamine into siliconized tubes. The elution solvent was removed by vacuum centrifugation, and the PCP was then resuspended in 100 μl of normal sheep serum. The amount of PCP in the samples was determined by radioimmunoassay as previously described (Proksch et al., 2000). Percentage recovery was about 80 to 95% (determined with serum samples spiked with [3H]PCP). PCP protein binding in serum samples (120 μl) was determined by equilibrium dialysis with a [3H]PCP tracer as previously described (Proksch et al., 2000).

After collection of blood, the brain and right testis were removed, quickly frozen in liquid nitrogen, and stored at ~80°C. The tissues were thawed on ice and homogenized in 5 vol of ice-cold water. Aliquots (200 μl) of the tissue homogenates were incubated with 300 μl of 8 M guanidine hydrochloride for 30 min. The homogenates were extracted, and PCP was quantified as described for serum samples. Percentage recovery of PCP from tissue samples was about 81 to 85%. The PCP concentrations in the tissue samples (uncorrected for the blood remaining in the tissue) were then determined using eq. 1:

\[
C_{\text{PCP}} = \frac{C_{\text{H}}}{V_{\text{H}}} \cdot (W_{\text{T}}/W_{\text{C}})
\]

where were recorded, and rats were monitored daily for the presence of stress-induced chromodacryorrhea.

**PCP and Anti-PCP mAb Administration.** PCP was prepared in a sterile saline solution such that a dose of 18 mg/kg/day (calculated as the free base) was delivered via subcutaneous osmotic minipump. The pumps were implanted between the scapulae of the rats under halothane anesthesia at approximately 10:00 AM on day 0 of the experiment. Because the t1/2Z of PCP is ~3.9 h in rats (Valentine et al., 1994), PCP concentrations should have reached steady-state concentrations at approximately 6:00 AM the morning after implantation of the pumps (i.e., ~4 h for pumping rate to become stable, plus four half-lives for PCP to reach steady-state concentrations). From ~7:00 to 11:00 AM the day after implanting pumps (experiment day 1), behavioral assessments were conducted (described in the following section). Immediately after the baseline behavior session, anti-PCP mAb or vehicle was infused via the jugular catheter at a rate of ~2 ml/min (8 ml total volume).
homogenization. More precise PCP concentrations were then calculated by correcting for the amount of PCP present in the blood contained in the tissue. Blood PCP concentrations were determined using an equation from Rowland and Tozer (1995). The corrected concentration of PCP in the tissues was calculated using the following equation: $C_{PCP_{cor}} = (C_{PCP} - C_b) \cdot (V_{b}) / (1 - (V_{b}) - (1 - C_b))$ (adapted from Khor et al., 1991). $C_{PCP_{cor}}$ and $C_b$ are the corrected tissue (ng/g) and blood (ng/ml) PCP concentrations, respectively, and $C_{PCP}$ is derived from eq. 1. The volume fraction of blood ($V_b$) remaining in brain and testis was obtained from Khor et al. (1991) and Everett et al. (1956), respectively.

**Statistical Analysis.** All statistical analyses were carried out with SigmaStat version 1.0 (SPSS Science, Chicago, IL). A two-way repeated measures ANOVA with dose group and treatment (pre- and post-treatment) as the main factors was conducted to determine differences in locomotor activity pre- and post-mAb treatments. A two-way ANOVA with dose group and day as the main factors was used to determine differences in body weight. For all pairwise comparisons, Tukey’s test was used. For serum and tissue PCP levels, a one-way ANOVA followed by Dunnett’s post hoc test was used to determine differences between controls and treatment groups. For the analysis of the results from the studies of changes in chromodacryorrhea, we used a Kruskal-Wallis one-way ANOVA followed by Dunn post hoc method for multiple comparisons with a control group. Statistical significance was defined as $p < 0.05$.

**Results**

**Effects of Saline and Anti-PCP mAb on PCP-Induced Locomotor Activity.** Figure 1 shows PCP-induced locomotor activity in rats for the 2 h before and the 2 h after treatment with saline or anti-PCP mAb. Statistical analysis of the locomotor activity showed an antibody dose by time interaction ($F = 3.4, df = 6, p < 0.001$). Pretreatment locomotor activity between mAb dose groups was not significantly different. However, there were significant differences in post-treatment locomotor activity between groups ($p < 0.05$). The post-treatment locomotor activity in the 1 mol Eq group was significantly different from the no mAb control group. In addition, locomotor activity after anti-PCP mAb administration was significantly decreased in all mAb treatment groups, compared with their pretreatment controls ($p < 0.05$), except for the saline-treated control group.

**Effects of Anti-PCP mAb on PCP-Induced Adverse Health Effects.** As an indicator of PCP effects on the general health of the rats, we measured body weight and monitored the rats for the presence of chromodacryorrhea over the course of the experiment. Figure 2 shows the effect of anti-PCP mAb on body weight in PCP-treated rats. All rats weighed ~280 to 300 g at the beginning of the experiment (day 0). The results are presented as the percentage of each rat’s control weight on day 0 of the experiment (before the PCP pump was implanted). Please note that the feeding regimen (three pellets of food per day) was adequate to maintain the rat’s weight, as shown in the saline-saline controls. All doses of anti-PCP mAb, except the 0.003 mol Eq (lowest) dose, protected rats from PCP-induced weight loss. Statistical analysis of the body weight data revealed no significant interaction between mAb dose group and day ($F = 1.35, df = 60, p = 0.057$); however, there was a significant mAb dose effect ($F = 26.48, df = 6, p < 0.001$). Body weight was significantly decreased in the PCP-saline group and in the PCP-0.003 mol Eq anti-PCP mAb group compared with other treatment groups ($p < 0.05$). The body weights of PCP-treated rats that received anti-PCP mAb at doses ranging from 0.01 to 1 mol Eq were not significantly different from control rats that received a saline infusion (without PCP) and a saline treatment on day 1 (saline-saline group, Fig. 2). The PCP-induced weight loss achieved maximum on about day 4 of the experiment. On this day, the mAb showed a dose response for protection against weight loss (Fig. 2, inset). On experiment days 4 through 7, the rats in the PCP-saline and PCP-0.003 mol Eq dose groups showed the most profound PCP-induced adverse effects. In fact, in each group, 25% of the rats died or had to be sacrificed for humane reasons. Consequently, we repeated the PCP-saline control experiment in a separate group of rats 3 months after the initial PCP-saline group (PCP-saline control 1 and 2; Fig. 2, inset) to ensure the reproducibility of our results. In both PCP-saline control groups, 1 of 4 of the animals died as a result of the PCP administration.

Chromodacryorrhea (or red tears) is a condition that occurs when Harderian gland secretions are increased in response to stress or disease (Harkness and Ridgway, 1980). In PCP-saline rats and the PCP-0.003 mol Eq rats, chromodacryorrhea was present for an average of 4 days (Fig. 3). In the other anti-PCP mAb-treated rat groups, duration was anti-PCP mAb dose-dependent (Fig. 3). Chromodacryorrhea was not observed in the saline-saline controls (data not shown). Statistical analysis showed a significant dose effect ($H = 12.1, df = 6, p = 0.003$). Significant differences ($p < 0.05$) from controls were achieved only in the 1 and 0.3 mol Eq anti-PCP mAb dose groups.

**PCP Serum Concentrations and Protein Binding.** PCP concentrations in serum (total, bound, and free) were measured at the end of the experiment (day 14 of the chronic PCP infusion) in all groups. Statistical analysis revealed a significant mAb dose effect ($F = 32.7, df = 6, p < 0.0001$). The concentration of free PCP was significantly decreased ($p < 0.05$) in all anti-PCP mAb dose groups except the 1 mol Eq group (Fig. 4). In this group, the amount of free PCP was significantly higher than in the saline controls ($p < 0.05$). Anti-PCP mAb dramatically increased the total PCP concent-
trations in the 0.3 and 1 mol Eq dose groups (4- and 10-fold, respectively) compared with PCP-saline-treated controls (Fig. 4, inset). PCP serum levels showed a significant positive correlation ($r = 0.997, p < 0.01$) with anti-PCP mAb dose; that is, as mAb dose increased, total serum PCP levels increased (data not shown).

At the end of the experiment (day 14), the percentage of PCP bound in the serum of the PCP-saline-treated groups was ~55% (Fig. 4, inset). This result is consistent with previous studies from our group (Valentine and Owens, 1996; Proksch et al., 2000). In the anti-PCP mAb treatment groups, the percentage of PCP bound in the serum was dependent on the dose of antibody. At the highest doses of anti-PCP mAb, the PCP binding was >95%. The percentage of PCP bound in the anti-PCP mAb-treated groups was significantly different ($p < 0.05$) from the PCP-saline groups in all cases, except for the PCP-0.003 mol Eq dose group. There was a significant...
correlation between PCP-induced effects and the percentage of unbound PCP ($p < 0.05$; data not shown). The correlation coefficients for percentage of unbound PCP versus locomotor activity, body weight, and chromodacryorrhea were 0.97, −0.98, and 0.95, respectively.

**Brain and Testis PCP Concentrations.** Figure 5 shows brain and testis PCP concentrations in each of the treatment groups on day 14 of the chronic PCP infusion. Statistical analysis revealed a significant mAb dose effect on brain ($F = 13.8$, df = 6, $p < 0.0001$) and testis ($F = 16.02$, df = 6, $p < 0.001$) PCP concentrations. Brain PCP concentrations were significantly decreased ($p < 0.05$) in all anti-PCP mAb treatment groups compared with PCP-saline-treated controls, except for the 0.003 mol Eq group (Fig. 5A). The largest decrease in PCP brain concentrations was in the 0.3 mol Eq group (70% reduction); however, the 0.3 mol Eq dose group was not statistically different from the 0.1 or 1 mol Eq dose groups. PCP concentrations in the testis were also significantly reduced ($p < 0.05$) after anti-PCP mAb treatment, except in the 0.003 mol Eq dose group (Fig. 5B).

**Discussion**

The development of pharmacotherapies for drug abuse has focused primarily on two specific medical indications: treatments for drug overdose and reducing or blocking self-administration. In reality, there are a wide range of health problems that result from chronic, excessive use of addictive drugs. We hypothesized that an anti-PCP mAb might provide a medication that would go beyond the usual medical paradigm for treating drug abuse. Thus, we examined the ability of a range of doses of anti-PCP mAb to effectively reduce or prevent adverse health effects resulting from chronic high-dose PCP treatment.

We think our hypothesis was confirmed by the finding that mAb doses ranging from 0.01 to 1 mol Eq produced significant improvements in PCP-induced behavior (Fig. 1), significant reductions in tissue concentrations (both brain and testes; Fig. 5), and improvements in the general health status of the animals (Figs. 2 and 3). These studies are consistent with an emerging paradigm for use of antibody therapy for drug abuse. For instance, other investigators using vaccines to produce an active immune response or passive administration of drug-specific antibodies for nicotine and cocaine have shown that the effectiveness of therapy is greater than would be expected based on calculated antibody capacity (Carrera et al., 2000; Kantak et al., 2000; Malin et al., 2002).

In addition to reducing brain concentrations, anti-PCP mAb also significantly decreased testis PCP concentrations at all doses except the 0.003 mol Eq dose. These results contrast with previous results from our laboratory in which a mol Eq dose of anti-PCP mAb resulted in only a 20% decrease in testis PCP concentrations on day 14. Although we cannot fully explain this discrepancy, we believe that improved precision of the analytical methods may partially explain this difference. Furthermore, previous studies from our laboratory have shown that anti-PCP Fab also significantly reduces testis PCP concentrations after an intravenous PCP dose (Valentine and Owens, 1996).

Our data show that the relationship between tissue and serum PCP concentrations was complex. Because the dose of PCP was constant, we expected to find mAb dose-dependent decreases in unbound PCP serum and PCP tissue concentrations. Although most of the pharmacokinetic data followed this trend, there were some exceptions. For example, in the 1 mol Eq group, the concentration of free serum PCP was significantly increased (relative to the PCP-saline-treated control group), even though the total serum PCP was >95% bound (Fig. 4). We have observed this effect on free PCP serum concentrations in previous pharmacokinetic studies with equimolar doses of anti-PCP Fab and mAb (Valentine and Owens, 1996; Proksch et al., 2000). We are currently conducting studies aimed at determining how the mAb handles an incoming dose of PCP in the presence of a saturating PCP dose to help elucidate the mechanism for these effects.

Despite the increased free serum PCP concentration, the 1 mol Eq dose of mAb was still able to significantly reduce PCP tissue concentrations relative to the PCP-saline control group. This appears to contradict a basic principle of pharmacology, which states that the unbound serum drug concentration is the most accurate predictor of drug response. Although the beneficial effects were highly correlated with the percentage of bound PCP, we think that brain PCP concentrations are also predictive of the effects of mAb. Our previous data (using the same PCP dosing regimen) show that a 1 mol Eq dose of this mAb decreases PCP levels in the brain to almost undetectable levels during the first 6 h after administration (Proksch et al., 2000). However, PCP levels increase to about 470 ng/g at 12 h after mAb administration and remain constant for at least 14 days, which is in perfect agreement with our current findings (brain PCP concentration = 497 ng/g at 14 days in the 1 mol Eq group). Thus, we believe that the mAb doses ranging from 0.01 to 1 mol Eq were sufficient to produce an initial rapid decrease in brain concentration. This would correlate with our locomotor activity results, which were obtained immediately after mAb ad-

![Fig. 5. PCP levels in brain (A) and testis (B) in rats treated with anti-PCP mAb during a continuous infusion of 19 ng/kg/day PCP. PCP was extracted from brain and testis and quantified by radioimmunoassay. Values represent the mean ± S.D. (n = 3–4 per group for anti-PCP mAb and n = 6 per group for the PCP-saline controls). Asterisks (*) indicate groups that were statistically different from the control group ($p < 0.05$).](image-url)
ministration. However, the ability of the mAb to keep brain concentrations low over the course of the experiment contributed to the continued maintenance of the rat’s health.

The beneficial effects of the treatment occurred at mAb doses that were always substantially below the body burden of PCP. Although we do not know the precise mechanisms for these profound changes, we know some of the important factors that contribute to these effects. First, the half-life for elimination of the antibody-PCP complex is about 15 days (“functional” \( t_{1/2,\text{ax}} = 15 \) days; Proksch et al., 2000), and this appears to be a significant factor in the prolonged action of the anti-PCP mAb. Second, because the anti-PCP mAb maintains such high serum protein binding, it is able to mobilize PCP from more rapidly equilibrating tissue beds. Our previous studies show that rapidly equilibrating organs appear to be preferentially protected (Valentine and Owens, 1996; Proksch et al., 2000). Another important aspect of this mechanism involves the change in brain clearance of the drug with and without antibody treatment. Without mAb treatment, protein binding is not a significant factor in PCP clearance from the blood to the brain (Valentine and Owens, 1996); however, with mAb treatment, PCP clearance changes from a nonrestrictive type to a restrictive type (Valentine and Owens, 1996). Although these explanations of the mechanism are not perfect, they do help in the interpretation of the complex effect that results from treatment with this mAb.

Another important factor in the ability of the anti-PCP mAb to reduce PCP-induced effects, even at low antibody doses, is attributable to the high affinity of the anti-PCP mAb (1.3 nM). Other studies have examined the effect of antibody affinity on drug redistribution (Ragusi et al., 1998). In these other studies, high-affinity anti-imipramine mAb (mAb/imipramine ratio of 100:1) was much more efficient than a low-affinity anti-imipramine mAb (mAb/imipramine ratio 1,000:1) at removing imipramine from the brain. Indeed, the brain area under the concentration-time curve (AUC) was about 40% lower in the high-affinity group compared with the low-affinity group.

Humans often repeatedly self-administer stimulants like PCP at great cost to their health (Walberg et al., 1983). Although we data suggest that the anti-PCP mAb may treat or prevent adverse effects of PCP abuse, it is unlikely to reduce craving for PCP. However, anti-PCP mAb may be useful in preventing relapse under certain circumstances. Our data suggest that whereas the highest (1 mol Eq) mAb dose is most effective at reducing PCP effects, the lower mAb doses resulted in lower brain PCP concentrations than the 1 mol Eq dose during chronic treatment. Thus, the use of lower mAb doses for treatment of chronic PCP use may be more beneficial to the brain. Scaling these rat data to humans, we can make the following prediction. A single 1-g dose of this anti-PCP mAb could significantly reduce the adverse effects of a 1.2 g/day binge use of PCP for up to 6 weeks. This prediction was based on the following assumptions. First, the dose of PCP (18 mg/kg/day) is the human equivalent of 1.26 g of PCP per day for an average adult male (18 mg/kg/day \( \times \) 70-kg human = 1.26 g/day). Second, the lowest effective dose of mAb in the rats was 15 mg/kg. This is equivalent to \(~1\) g total dose of mAb in a 70-kg human. Third, the duration of effect in humans is based on the biological half-life of mouse monoclonal IgG in rats (8 days; Bazin-Redureau et al., 1997), scaled up to the biological half-life of a human IgG in humans (21–25 days; Knapp and Colburn, 1990). If our predictions are accurate, this antibody treatment would allow extended intervals between doses (if a second dose were required) and would reduce the need for patient compliance. Furthermore, the use of a human anti-PCP mAb would reduce or prevent the potential for allergic reactions.

In conclusion, anti-PCP mAb significantly reduced the negative impact of excessive PCP dosing on a wide range of PCP-induced effects for a prolonged period in the rats. The protective effects of the mAb were dependent on the dose of mAb and doses as low as 1/100th the molar equivalent amount of the PCP body burden were still medically effective. Surmountability of antidrug antibody effects (by increasing drug administration) is an important issue that may limit the potential usefulness of immunotherapy for drug abuse. However, studies from our laboratory and others (Carrera et al., 2000; Kantak et al., 2000; Malin et al., 2002) have convincingly shown that antibody capacity is not the limiting factor in reducing drug effects. Thus, treatment with mAb medications can have medically important outcomes without neutralization of the entire dose of the offending drug. With a combination of other treatment strategies such as counseling, immunotherapy for drug abuse may help even the most seriously addicted patients.

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References


Address correspondence to: Dr. S. Michael Owens, Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot 611, Little Rock, AR 72205. E-mail: owenssamuelm@uams.edu