DRUG METABOLISM & DISPOSITION

Correction to "A Recombinant Humanized Anti-Cocaine Monoclonal Antibody Inhibits the Distribution of Cocaine to the Brain in Rats"

Andrew B. Norman and William J. Ball, the senior authors of the above article [Norman AB, Gooden FCT, Tabet MR, and Ball WJ (2014) *Drug Metab Dispos* **42**:1125–1131; doi:10.1124/dmd.114.057034] have recently identified data entry and data analysis errors.

The article's discussion of the cloning of the monoclonal antibody (mAb) 2E2, the re-engineering of the light chain to a more fully human sequence, and the high level production of recombinant h2E2 from CHO cells remains unchanged.

The authors are unable to locate the raw data liquid scintillation counter printouts that would confirm the data originally presented in Figure 1. However, they have repeated the [^{3}H]cocaine binding studies using a similar protocol to that reported. They find values for the K_d of [^{3}H]cocaine for the recombinant h2E2 in the range of approximately 4.1 to 16 nM. In addition they have independently confirmed h2E2's low nanomolar affinity for cocaine through the use of a fluorescence assay [Kirley and Norman (2015) *Hum Vaccin Immunother* **11:** 458–467].

A reanalysis of the original ELISA plate data is shown in Table 1. The relative binding affinities now include mean and S.E.M. values. The conclusion that h2E2 retains specificity for cocaine over its inactive metabolites and retains high affinity for cocaethylene remains unchanged.

Reanalysis of the raw data for Figure 2 shows that the calculated pharmacokinetic parameters are similar to those originally reported. The calculated distribution half-life ($t_{1/2\alpha}$) of h2E2 was 13.5 hours, the terminal elimination half-life ($t_{1/2\beta}$) was 7.8 days, and the volume of distribution (V_{dss}) was 0.2 l/kg.

For Figure 3, a reanalysis of the original GC/MS data generated concentration versus time plots similar to those initially reported. The key conclusions that h2E2 sequesters cocaine in the plasma and antagonizes cocaine entry into the brain in rats remains unchanged. This was demonstrated by the h2E2-induced 14.7-fold increase in the plasma cocaine area under the time-concentration curve (AUC) (Fig. 3A) and the 94% decrease in the brain cocaine AUC (Fig. 3B).

For Figure 4, a reanalysis of the original GC/MS data demonstrated that the measurements of BE concentrations in the plasma samples were not sufficiently reliable to draw conclusions about the effects of h2E2 on the formation of BE. In the brain, BE concentrations were too low to be reliably detected in the absence and presence of h2E2. The minor conclusion that cocaine may be metabolized in the brain in rats is not substantiated by the reanalysis.

The revised Table 2 contains the reanalysis of the pharmacokinetics of cocaine in the presence and absence of h2E2 from the fits to the data shown in Figure 3A and B. It should be noted that the terminal elimination half-life of cocaine from plasma was increased 1.4-fold in the presence of h2E2.

The authors apologize for these errors. An investigation by the University of Cincinnati determined that AB Norman, WJ Ball, and FCT Gooden did not take part in and were unaware of any inappropriate data handling.

The authors acknowledge the efforts of Hanna N. Wetzel in the data reanalysis and Dr. Rose P. Webster and Fatima O. Saeed for repeating the [^{3}H]cocaine binding studies.

TABLE 1

Reanalysis of the original ELISA plate data for the relative binding affinities of monoclonal antibodies 2E2 and h2E2 for cocaine and its metabolites

The relative binding affinities (RBAs) were measured using a competition enzyme-linked immunosorbent assay, as described in *Materials and Methods*. The measured IC_{50} values for each metabolite were compared with that of cocaine, which was designated a RBA of 1. Values higher or lower than 1 indicate, respectively, a lower or higher affinity for h2E2 than that of cocaine.

Metabolite	2E2	h2E2
Cocaine	1 ± 0	1 ± 0
Cocaethylene	0.5 ± 0.2	0.3 ± 0.03
Norcocaine	142 ± 71	87 ± 34
Benzoylecgonine	10 ± 2	6.8 ± 0.3
Ecgonine methyl ester	2972 ± 824	1896 ± 793
Ecgonine	442 ± 64	273 ± 8

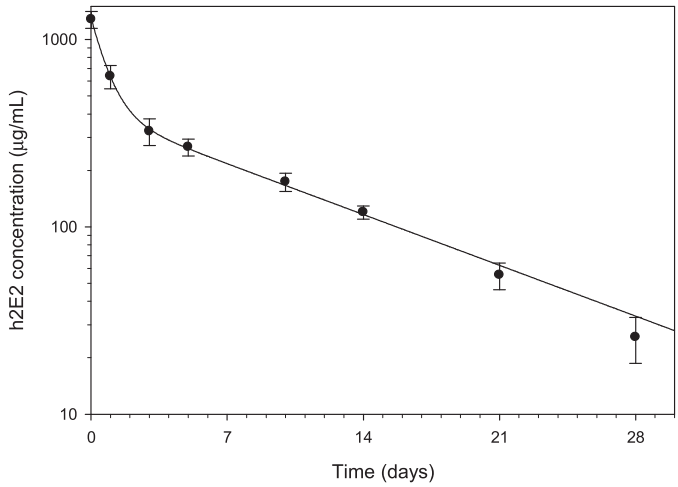

Fig. 2. The pharmacokinetics of the anti-cocaine mAb h2E2 in rats. Animals received an i.v. infusion of 120 mg/kg h2E2. Samples of blood (10 μl) were obtained from tail veins at the indicated times after completion of the mAb infusion. Concentrations of h2E2 in blood were determined using an ELISA. Data points represent the mean ± S.E. M. from four rats. The V_{dss} was 0.2 l/kg. A two-compartment model with a $t_{1/2\alpha}$ of 13.5 hours described the distribution phase, and a $t_{1/2\beta}$ of 7.8 days described the elimination phase, represented by the best-fit regression line.

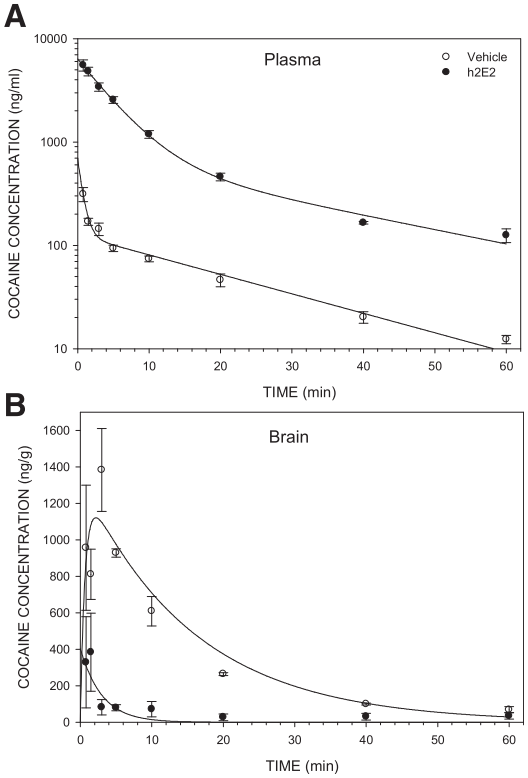

Fig. 3. The effect of h2E2 on the pharmacokinetics of cocaine in plasma (A) and brain (B) in rats. Rats received an i.v. infusion of 120 mg/kg h2E2. One hour later the rats received an i.v. injection of cocaine HCl (0.56 mg/kg). The animals were sacrificed at the indicated times, and blood and the brain were collected. Cocaine concentrations were determined by GC/MS. Each data point represents the mean ± S.E.M. from three rats. In the absence of h2E2 (open circles), the cocaine concentration-time profile in plasma (A) was described by a two-compartment pharmacokinetic model with a $t_{1/2\alpha}$ of 0.5 minute and a $t_{1/2\beta}$ of 16 minutes. In the presence of h2E2 (closed circles), a two-compartment pharmacokinetic model indicated a $t_{1/2\alpha}$ of 3.2 minutes and a $t_{1/2\beta}$ of 21.7 minutes. h2E2 produced a 14.7-fold increase in the area under the plasma cocaine AUC. The V_{dss} in the absence and presence of h2E2 was 3.5 and 0.2 l/kg, respectively. In the brain (B) in the absence of h2E2 (open circles), a two-compartment pharmacokinetic model with an AUC of 20,162 (ng/g) × minutes described the cocaine concentration-time profile. In the presence of h2E2 (closed circles), a two-compartment pharmacokinetic model with an AUC of 1,219 (ng/g) × minutes described the cocaine concentration-time profile. h2E2 produced a 94% decrease in the brain cocaine AUC.

TABLE 2

Reanalysis of the pharmacokinetics of cocaine in the presence and absence of h2E2 from the fits to the data shown in Fig. 3, A and B

The parameter estimates were generated using the program WinNonLin from the models shown in Figure 3, A and B. + Represents the fold increase from the control values; − represents the percent decrease from control values.

Parameters	Plasma			Brain		
	Vehicle	h2E2	Change	Vehicle	h2E2	Change
AUC (min*ng/ml)	3,282	48,101	+14.7-fold	20,162	1,219	-94%
$t_{1/2\alpha}$ (minutes)	0.5	3.2	+6.5-fold			
$t_{1/2\beta}$ (minutes)	16.0	21.7	+1.4-fold			
Cl (l/min/kg)	0.17	0.012	-93%			
V_{dss} (l/kg)	3.5	0.2	-94%			